Preface

Biology is designed for multi-semester biology courses for science majors. It is grounded on an evolutionary basis and includes exciting features that highlight careers in the biological sciences and everyday applications of the concepts at hand. To meet the needs of today's instructors and students, some content has been strategically condensed while maintaining the overall scope and coverage of traditional texts for this course. Instructors can customize the book, adapting it to the approach that works best in their classroom. Biology also includes an innovative art program that incorporates critical thinking and clicker questions to help students understand—and apply—key concepts.

Welcome to *Biology*, an OpenStax resource. This textbook was written to increase student access to high-quality learning materials, maintaining highest standards of academic rigor at little to no cost.

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Format

You can access this textbook for free in web view or PDF through openstax.org, and in low-cost print and iBooks editions.

About Biology

Biology is designed to cover the scope and sequence requirements of a typical two-semester biology course for science majors. The text provides comprehensive coverage of foundational research and core biology concepts through an evolutionary lens. *Biology* includes rich features that engage students in scientific inquiry, highlight careers in the biological sciences, and offer everyday applications. The book also includes clicker questions to help students understand—and apply—key concepts.

Coverage and Scope

In developing *Biology*, we listened to hundreds of General Biology instructors who readily provided feedback about their courses, students, challenges, and hopes for innovation. The expense of textbooks and related items did prove to be a barrier to learning. But more importantly, these teachers suggested improvements for the textbook, which would ultimately lead to more meaningful and memorable learning experiences for students.

The result is a book that addresses a core organizational reality of the course and its materials—the sheer breadth of the topical coverage. We provide a thorough treatment of biology's foundational concepts while condensing selected topics in response to the market's request for a textbook with a scope that is manageable for instructors and students alike. We also strive to make biology, as a discipline, interesting and accessible to students. In addition to a comprehensive coverage of core concepts and foundational research, we have incorporated features that draw learners into the discipline in meaningful ways.

The pedagogical choices, chapter arrangements, and learning objective fulfillment were developed and vetted with the feedback of another one hundred reviewers, who thoroughly read the material and offered detailed critical commentary.

> Unit 1: **The Chemistry of Life**. Our opening unit introduces students to the sciences, including the scientific method and the fundamental concepts of chemistry and physics that provide a framework within which learners comprehend biological processes.

Unit 2: **The Cell**. Students will gain solid understanding of the structures, functions, and processes of the most basic unit of life: the cell.

Unit 3: **Genetics**. Our comprehensive genetics unit takes learners from the earliest experiments that revealed the basis of genetics through the intricacies of DNA to current applications in the emerging studies of biotechnology and genomics.

Unit 4: **Evolutionary Processes**. The core concepts of evolution are discussed in this unit with examples illustrating evolutionary processes. Additionally, the evolutionary basis of biology reappears throughout the textbook in general discussion and is reinforced through special call-out features highlighting specific evolution-based topics.

Unit 5: **Biological Diversity**. The diversity of life is explored with detailed study of various organisms and discussion of emerging phylogenetic relationships. This unit moves from viruses to living organisms like bacteria, discusses the organisms formerly grouped as protists, and devotes multiple chapters to plant and animal life.

Unit 6: **Plant Structure and Function**. Our plant unit thoroughly covers the fundamental knowledge of plant life essential to an introductory biology course.

Unit 7: **Animal Structure and Function**. An introduction to the form and function of the animal body is followed by chapters on specific body systems and processes. This unit touches on the biology of all organisms while maintaining an engaging focus on human anatomy and physiology that helps students connect to the topics.

Unit 8: **Ecology**. Ecological concepts are broadly covered in this unit, with features highlighting localized, real-world issues of conservation and biodiversity.

Pedagogical Foundation and Features

Biology is grounded in a solid scientific base, with features that engage the students in scientific inquiry, including:

Evolution Connection features uphold the importance of evolution to all biological study through discussions like "The Evolution of Metabolic Pathways" and "Algae and Evolutionary Paths to Photosynthesis."

Scientific Method Connection call-outs walk students through actual or thought experiments that elucidate the steps of the scientific process as applied to the topic. Features include "Determining the Time Spent in Cell Cycle Stages" and "Testing the Hypothesis of Independent Assortment."

Career Connection features present information on a variety of careers in the biological sciences, introducing students to the educational requirements and day-to-day work life of a variety of professions, such as microbiologist, ecologist, neurologist, and forensic scientist.

Everyday Connection features tie biological concepts to emerging issues and discuss science in terms of everyday life. Topics include "Chesapeake Bay" and "Can Snail Venom Be Used as a Pharmacological Pain Killer?"

Art and Animations That Engage

Our art program takes a straightforward approach designed to help students learn the concepts of biology through simple, effective illustrations, photos, and micrographs. *Biology* also incorporates links to relevant animations and interactive exercises that help bring biology to life for students.

Art Connection features call out core figures in each chapter for student study. Questions about key figures, including clicker questions that can be used in the classroom, engage students' critical thinking to ensure genuine understanding.

Link to Learning features direct students to online interactive exercises and animations to add a fuller context to core content.

Additional Resources

Student and Instructor Resources

We've compiled additional resources for both students and instructors, including Getting Started Guides, an instructor solution manual, supplemental test items, and PowerPoint slides. Instructor resources require a verified instructor account, which can be requested on your openstax.org log-in. Take advantage of these resources to supplement your OpenStax book.

Partner Resources

OpenStax Partners are our allies in the mission to make high-quality learning materials affordable and accessible to students and instructors everywhere. Their tools integrate seamlessly with our OpenStax titles at a low cost. To access the partner resources for your text, visit your book page on openstax.org.

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Introduction
class="introduction"

(a) Nasal sinus cells (viewed with a light microscope), (b) onion cells (viewed with a light microscope), and (c) *Vibrio tasmaniensis* bacterial cells (seen through a scanning electron microscope) are from very different organisms, yet all share certain characteristics of basic cell structure. (credit a: modification of work by Ed Uthman, MD; credit b: modification of work by Umberto Salvagnin; credit c:

(a) 10 μm (b) 50 μm (c) 500 nm
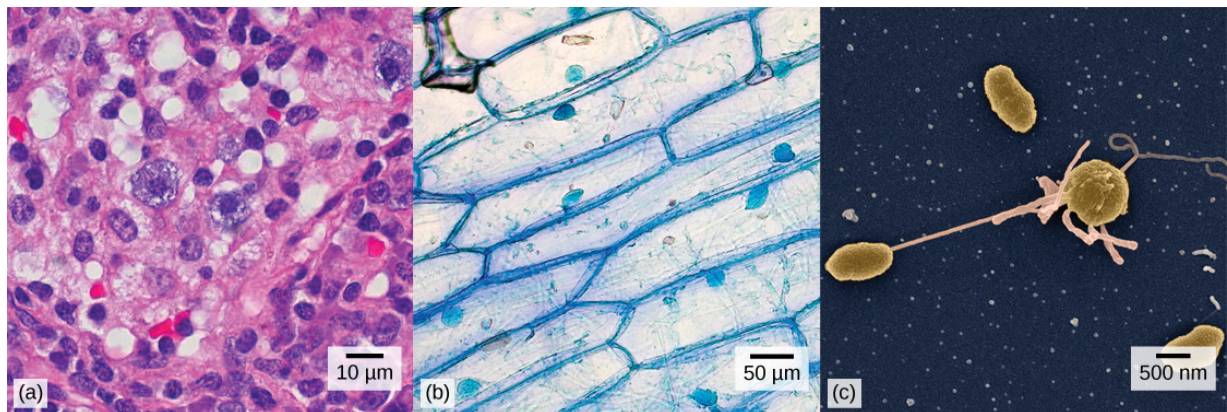
Close your eyes and picture a brick wall. What is the basic building block of that wall? A single brick, of course. Like a brick wall, your body is composed of basic building blocks, and the building blocks of your body are cells.

Your body has many kinds of cells, each specialized for a specific purpose. Just as a home is made from a variety of building materials, the human body is constructed from many cell types. For example, epithelial cells protect the surface of the body and cover the organs and body cavities within. Bone cells help to support and protect the body. Cells of the immune

system fight invading bacteria. Additionally, blood and blood cells carry nutrients and oxygen throughout the body while removing carbon dioxide. Each of these cell types plays a vital role during the growth, development, and day-to-day maintenance of the body. In spite of their enormous variety, however, cells from all organisms—even ones as diverse as bacteria, onion, and human—share certain fundamental characteristics.

Studying Cells
By the end of this section, you will be able to:

- Describe the role of cells in organisms
- Compare and contrast light microscopy and electron microscopy
- Summarize cell theory

A cell is the smallest unit of a living thing. A living thing, whether made of one cell (like bacteria) or many cells (like a human), is called an organism. Thus, cells are the basic building blocks of all organisms.

Several cells of one kind that interconnect with each other and perform a shared function form tissues, several tissues combine to form an organ (your stomach, heart, or brain), and several organs make up an organ system (such as the digestive system, circulatory system, or nervous system). Several systems that function together form an organism (like a human being). Here, we will examine the structure and function of cells.

There are many types of cells, all grouped into one of two broad categories: prokaryotic and eukaryotic. For example, both animal and plant cells are classified as eukaryotic cells, whereas bacterial cells are classified as prokaryotic. Before discussing the criteria for determining whether a cell is prokaryotic or eukaryotic, let's first examine how biologists study cells.

Microscopy

Cells vary in size. With few exceptions, individual cells cannot be seen with the naked eye, so scientists use microscopes (micro- = "small"; -scope = "to look at") to study them. A **microscope** is an instrument that magnifies an object. Most photographs of cells are taken with a microscope, and these images can also be called micrographs.

The optics of a microscope's lenses change the orientation of the image that the user sees. A specimen that is right-side up and facing right on the microscope slide will appear upside-down and facing left when viewed through a microscope, and vice versa. Similarly, if the slide is moved left while looking through the microscope, it will appear to move right, and if

moved down, it will seem to move up. This occurs because microscopes use two sets of lenses to magnify the image. Because of the manner by which light travels through the lenses, this system of two lenses produces an inverted image (binocular, or dissecting microscopes, work in a similar manner, but include an additional magnification system that makes the final image appear to be upright).

Light Microscopes

To give you a sense of cell size, a typical human red blood cell is about eight millionths of a meter or eight micrometers (abbreviated as eight μm) in diameter; the head of a pin of is about two thousandths of a meter (two mm) in diameter. That means about 250 red blood cells could fit on the head of a pin.

Most student microscopes are classified as **light microscopes** ([link]**a**). Visible light passes and is bent through the lens system to enable the user to see the specimen. Light microscopes are advantageous for viewing living organisms, but since individual cells are generally transparent, their components are not distinguishable unless they are colored with special stains. Staining, however, usually kills the cells.

Light microscopes commonly used in the undergraduate college laboratory magnify up to approximately 400 times. Two parameters that are important in microscopy are magnification and resolving power. Magnification is the process of enlarging an object in appearance. Resolving power is the ability of a microscope to distinguish two adjacent structures as separate: the higher the resolution, the better the clarity and detail of the image. When oil immersion lenses are used for the study of small objects, magnification is usually increased to 1,000 times. In order to gain a better understanding of cellular structure and function, scientists typically use electron microscopes.
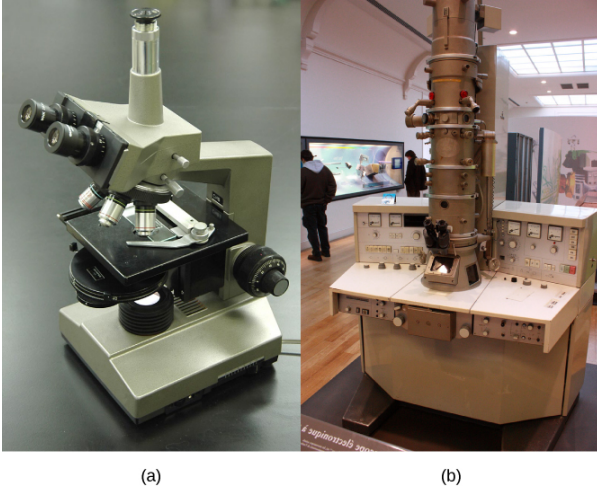
(a) Most light microscopes used in a college biology lab can magnify cells up to approximately 400 times and have a resolution of about 200 nanometers. (b) Electron microscopes provide a much higher magnification, 100,000x, and a have a resolution of 50 picometers. (credit a: modification of work by "GcG"/Wikimedia Commons; credit b: modification of work by Evan Bench)

Electron Microscopes

In contrast to light microscopes, **electron microscopes** ([link]**b**) use a beam of electrons instead of a beam of light. Not only does this allow for higher magnification and, thus, more detail ([link]), it also provides higher resolving power. The method used to prepare the specimen for viewing with an electron microscope kills the specimen. Electrons have short

wavelengths (shorter than photons) that move best in a vacuum, so living cells cannot be viewed with an electron microscope.

In a scanning electron microscope, a beam of electrons moves back and forth across a cell's surface, creating details of cell surface characteristics. In a transmission electron microscope, the electron beam penetrates the cell and provides details of a cell's internal structures. As you might imagine, electron microscopes are significantly more bulky and expensive than light microscopes.

(a) These *Salmonella* bacteria appear as tiny purple dots when viewed with a light microscope. (b) This scanning electron microscope micrograph shows *Salmonella* bacteria (in red) invading human cells (yellow). Even though subfigure (b) shows a different *Salmonella* specimen than subfigure (a), you can still observe the comparative increase in magnification and detail. (credit a: modification of work by CDC/Armed Forces Institute of Pathology, Charles N. Farmer, Rocky Mountain Laboratories; credit b: modification of work by NIAID, NIH; scale-bar data from Matt Russell)

Cell Theory

The microscopes we use today are far more complex than those used in the 1600s by Antony van Leeuwenhoek, a Dutch shopkeeper who had great skill in crafting lenses. Despite the limitations of his now-ancient lenses, van Leeuwenhoek observed the movements of protista (a type of single-celled organism) and sperm, which he collectively termed "animalcules."

In a 1665 publication called *Micrographia*, experimental scientist Robert Hooke coined the term "cell" for the box-like structures he observed when viewing cork tissue through a lens. In the 1670s, van Leeuwenhoek discovered bacteria and protozoa. Later advances in lenses, microscope construction, and staining techniques enabled other scientists to see some components inside cells.

By the late 1830s, botanist Matthias Schleiden and zoologist Theodor Schwann were studying tissues and proposed the **unified cell theory**, which states that all living things are composed of one or more cells, the cell is the basic unit of life, and new cells arise from existing cells. Rudolf Virchow later made important contributions to this theory.

Note:

Career Connection
Cytotechnologist
Have you ever heard of a medical test called a Pap smear ([link])? In this test, a doctor takes a small sample of cells from the uterine cervix of a patient and sends it to a medical lab where a cytotechnologist stains the cells and examines them for any changes that could indicate cervical cancer or a microbial infection.

Cytotechnologists (cyto- = "cell") are professionals who study cells via microscopic examinations and other laboratory tests. They are trained to determine which cellular changes are within normal limits and which are abnormal. Their focus is not limited to cervical cells; they study cellular specimens that come from all organs. When they notice abnormalities, they consult a pathologist, who is a medical doctor who can make a clinical diagnosis.

Cytotechnologists play a vital role in saving people's lives. When abnormalities are discovered early, a patient's treatment can begin sooner, which usually increases the chances of a successful outcome.
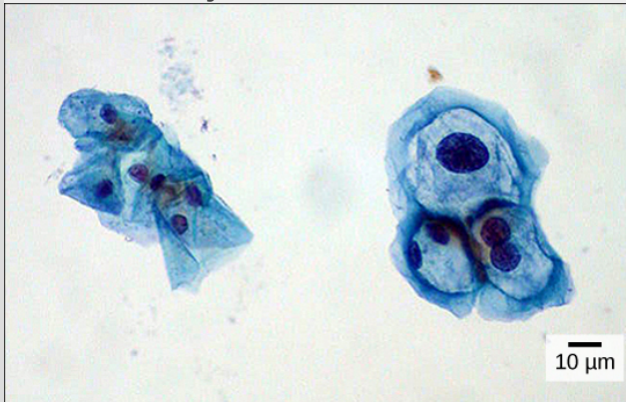
These uterine cervix cells, viewed through a light microscope, were obtained from a Pap smear. Normal cells are on the left. The cells on the right are infected with human papillomavirus (HPV). Notice that the infected cells are larger; also, two of these cells each have two nuclei instead of one, the normal number. (credit:

Section Summary

A cell is the smallest unit of life. Most cells are so tiny that they cannot be seen with the naked eye. Therefore, scientists use microscopes to study cells. Electron microscopes provide higher magnification, higher resolution, and more detail than light microscopes. The unified cell theory states that all organisms are composed of one or more cells, the cell is the basic unit of life, and new cells arise from existing cells.

Review Questions

Exercise:

Problem:

When viewing a specimen through a light microscope, scientists use _____ to distinguish the individual components of cells.

    a. a beam of electrons
    b. radioactive isotopes
    c. special stains
    d. high temperatures

Solution:

C

Exercise:

Problem: The _____ is the basic unit of life.

   a. organism
   b. cell
   c. tissue
   d. organ

Solution:

B

Free Response

Exercise:

Problem:

In your everyday life, you have probably noticed that certain instruments are ideal for certain situations. For example, you would use a spoon rather than a fork to eat soup because a spoon is shaped for scooping, while soup would slip between the tines of a fork. The use of ideal instruments also applies in science. In what situation(s) would the use of a light microscope be ideal, and why?

Solution:

A light microscope would be ideal when viewing a small living organism, especially when the cell has been stained to reveal details.

Exercise:

Problem:

In what situation(s) would the use of a scanning electron microscope be ideal, and why?

Solution:

A scanning electron microscope would be ideal when you want to view the minute details of a cell's surface, because its beam of electrons moves back and forth over the surface to convey the image.

Exercise:

Problem:

In what situation(s) would a transmission electron microscope be ideal, and why?

Solution:

A transmission electron microscope would be ideal for viewing the cell's internal structures, because many of the internal structures have membranes that are not visible by the light microscope.

Exercise:

Problem:

What are the advantages and disadvantages of each of these types of microscopes?

Solution:

The advantages of light microscopes are that they are easily obtained, and the light beam does not kill the cells. However, typical light microscopes are somewhat limited in the amount of detail they can reveal. Electron microscopes are ideal because you can view intricate details, but they are bulky and costly, and preparation for the microscopic examination kills the specimen.

Glossary

cell theory
    see unified cell theory

electron microscope
> an instrument that magnifies an object using a beam of electrons
> passed and bent through a lens system to visualize a specimen

light microscope
> an instrument that magnifies an object using a beam visible light
> passed and bent through a lens system to visualize a specimen

microscope
> an instrument that magnifies an object

unified cell theory
> a biological concept that states that all organisms are composed of one
> or more cells; the cell is the basic unit of life; and new cells arise from
> existing cells

Prokaryotic Cells
By the end of this section, you will be able to:

- Name examples of prokaryotic and eukaryotic organisms
- Compare and contrast prokaryotic cells and eukaryotic cells
- Describe the relative sizes of different kinds of cells
- Explain why cells must be small

Cells fall into one of two broad categories: prokaryotic and eukaryotic. Only the predominantly single-celled organisms of the domains Bacteria and Archaea are classified as prokaryotes (pro- = "before"; -kary- = "nucleus"). Animals, plants, fungi, and protists are all eukaryotes (eu- = "true") and are made up of eukaryotic cells.

Components of Prokaryotic Cells

All cells share four common components: 1) a plasma membrane, an outer covering that separates the cell's interior from its surrounding environment; 2) cytoplasm, consisting of a jelly-like cytosol within the cell in which other cellular components are found; 3) DNA, the genetic material of the cell; and 4) ribosomes, which synthesize proteins. However, prokaryotes differ from eukaryotic cells in several ways.

A **prokaryote** is a simple, mostly single-celled (unicellular) organism that lacks a nucleus, or any other membrane-bound organelle. We will shortly come to see that this is significantly different in eukaryotes. Prokaryotic DNA is found in a central part of the cell: the **nucleoid** ([link]).
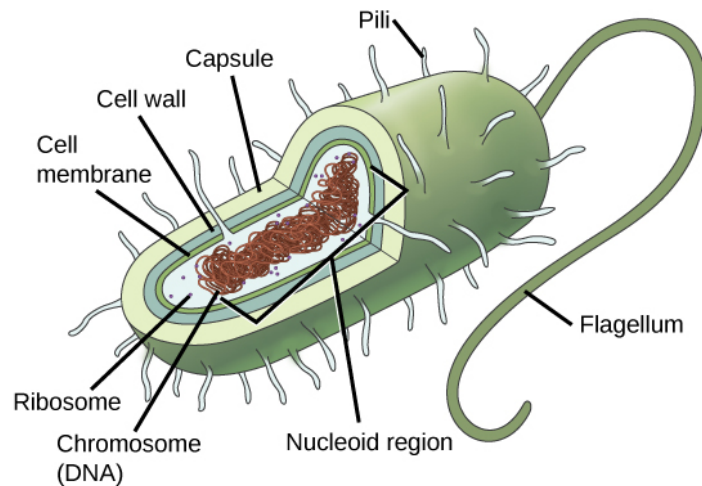
This figure shows the generalized structure of a prokaryotic cell. All prokaryotes have chromosomal DNA localized in a nucleoid, ribosomes, a cell membrane, and a cell wall. The other structures shown are present in some, but not all, bacteria.

Most prokaryotes have a peptidoglycan cell wall and many have a polysaccharide capsule ([link]). The cell wall acts as an extra layer of protection, helps the cell maintain its shape, and prevents dehydration. The capsule enables the cell to attach to surfaces in its environment. Some prokaryotes have flagella, pili, or fimbriae. Flagella are used for locomotion. Pili are used to exchange genetic material during a type of reproduction called conjugation. Fimbriae are used by bacteria to attach to a host cell.

Note:
Career Connection
Microbiologist
The most effective action anyone can take to prevent the spread of contagious illnesses is to wash his or her hands. Why? Because microbes

(organisms so tiny that they can only be seen with microscopes) are ubiquitous. They live on doorknobs, money, your hands, and many other surfaces. If someone sneezes into his hand and touches a doorknob, and afterwards you touch that same doorknob, the microbes from the sneezer's mucus are now on your hands. If you touch your hands to your mouth, nose, or eyes, those microbes can enter your body and could make you sick.

However, not all microbes (also called microorganisms) cause disease; most are actually beneficial. You have microbes in your gut that make vitamin K. Other microorganisms are used to ferment beer and wine. Microbiologists are scientists who study microbes. Microbiologists can pursue a number of careers. Not only do they work in the food industry, they are also employed in the veterinary and medical fields. They can work in the pharmaceutical sector, serving key roles in research and development by identifying new sources of antibiotics that could be used to treat bacterial infections.

Environmental microbiologists may look for new ways to use specially selected or genetically engineered microbes for the removal of pollutants from soil or groundwater, as well as hazardous elements from contaminated sites. These uses of microbes are called bioremediation technologies. Microbiologists can also work in the field of bioinformatics, providing specialized knowledge and insight for the design, development, and specificity of computer models of, for example, bacterial epidemics.

Cell Size

At 0.1 to 5.0 μm in diameter, prokaryotic cells are significantly smaller than eukaryotic cells, which have diameters ranging from 10 to 100 μm ([link]). The small size of prokaryotes allows ions and organic molecules that enter them to quickly diffuse to other parts of the cell. Similarly, any wastes produced within a prokaryotic cell can quickly diffuse out. This is not the case in eukaryotic cells, which have developed different structural adaptations to enhance intracellular transport.
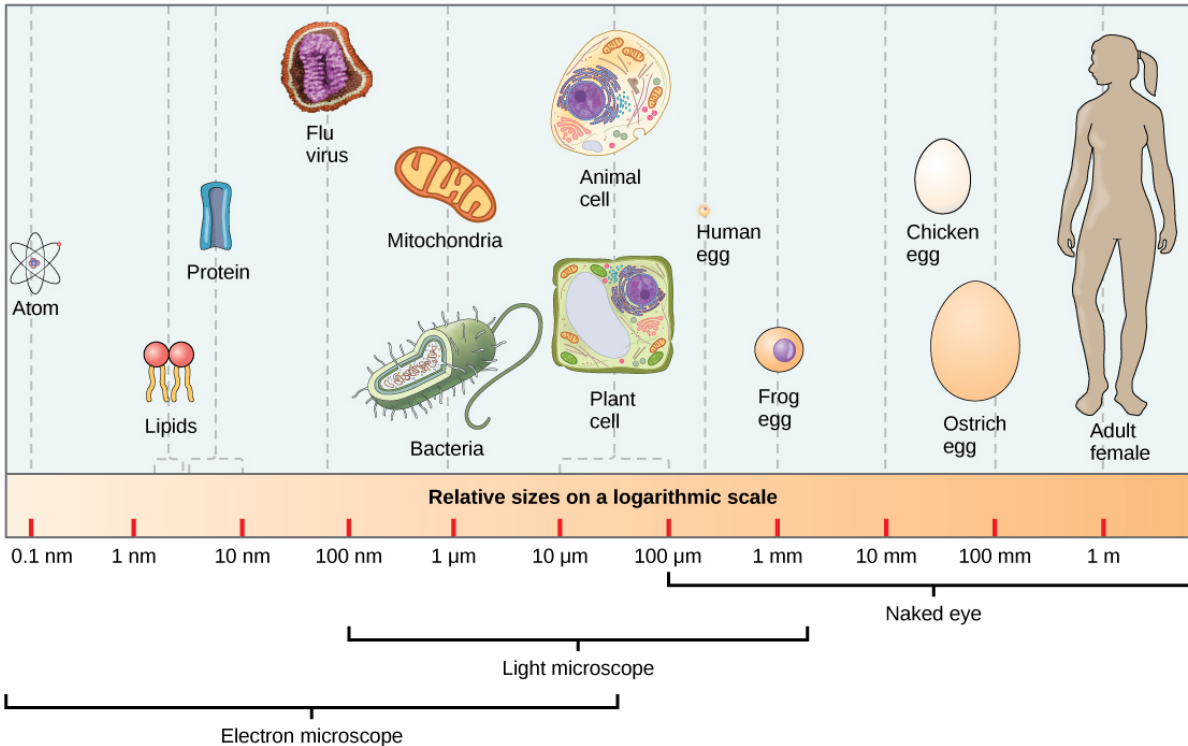
This figure shows relative sizes of microbes on a logarithmic scale (recall that each unit of increase in a logarithmic scale represents a 10-fold increase in the quantity being measured).

Small size, in general, is necessary for all cells, whether prokaryotic or eukaryotic. Let's examine why that is so. First, we'll consider the area and volume of a typical cell. Not all cells are spherical in shape, but most tend to approximate a sphere. You may remember from your high school geometry course that the formula for the surface area of a sphere is $4\pi r^2$, while the formula for its volume is $4\pi r^3/3$. Thus, as the radius of a cell increases, its surface area increases as the square of its radius, but its volume increases as the cube of its radius (much more rapidly). Therefore, as a cell increases in size, its surface area-to-volume ratio decreases. This same principle would apply if the cell had the shape of a cube ([link]). If the cell grows too large, the plasma membrane will not have sufficient surface area to support the rate of diffusion required for the increased volume. In other words, as a cell grows, it becomes less efficient. One way to become more efficient is to divide; another way is to develop organelles that

perform specific tasks. These adaptations lead to the development of more sophisticated cells called eukaryotic cells.
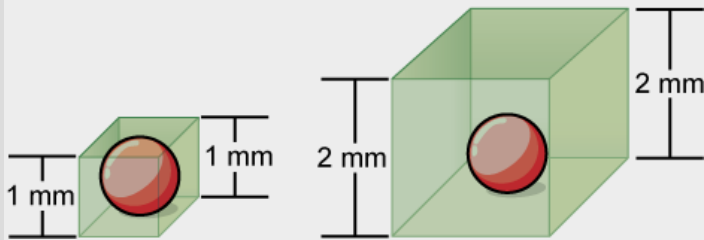
Notice that as a cell increases in size, its surface area-to-volume ratio decreases. When there is insufficient surface area to support a cell's increasing volume, a cell will either divide or die. The cell on the left has a volume of 1 mm^3 and a surface area of 6 mm^2, with a surface area-to-volume ratio of 6 to 1, whereas the cell on the right has a volume of 8 mm^3 and a surface area of 24 mm^2, with a surface area-to-volume ratio of 3 to 1.

Prokaryotic cells are much smaller than eukaryotic cells. What advantages might small cell size confer on a cell? What advantages might large cell size have?

Section Summary

Prokaryotes are predominantly single-celled organisms of the domains Bacteria and Archaea. All prokaryotes have plasma membranes, cytoplasm, ribosomes, and DNA that is not membrane-bound. Most have peptidoglycan cell walls and many have polysaccharide capsules. Prokaryotic cells range in diameter from 0.1 to 5.0 μm.

As a cell increases in size, its surface area-to-volume ratio decreases. If the cell grows too large, the plasma membrane will not have sufficient surface area to support the rate of diffusion required for the increased volume.

Art Connections

Exercise:

Problem:

[link] Prokaryotic cells are much smaller than eukaryotic cells. What advantages might small cell size confer on a cell? What advantages might large cell size have?

Solution:

[link] Substances can diffuse more quickly through small cells. Small cells have no need for organelles and therefore do not need to expend energy getting substances across organelle membranes. Large cells have organelles that can separate cellular processes, enabling them to build molecules that are more complex.

Review Questions

Exercise:

Problem:

Prokaryotes depend on _____ to obtain some materials and to get rid of wastes.

    a. ribosomes

b. flagella
c. cell division
d. diffusion

Solution:

D

Exercise:

Problem: Bacteria that lack fimbriae are less likely to _____.

a. adhere to cell surfaces
b. swim through bodily fluids
c. synthesize proteins
d. retain the ability to divide

Solution:

A

Free Response

Exercise:

Problem:

Antibiotics are medicines that are used to fight bacterial infections. These medicines kill prokaryotic cells without harming human cells. What part or parts of the bacterial cell do you think antibiotics target? Why?

Solution:

The cell wall would be targeted by antibiotics as well as the bacteria's ability to replicate. This would inhibit the bacteria's ability to

reproduce, and it would compromise its defense mechanisms.

Exercise:

Problem: Explain why not all microbes are harmful.

Solution:

Some microbes are beneficial. For instance, *E. coli* bacteria populate the human gut and help break down fiber in the diet. Some foods such as yogurt are formed by bacteria.

Glossary

nucleoid
    central part of a prokaryotic cell in which the chromosome is found

prokaryote
    unicellular organism that lacks a nucleus or any other membrane-bound organelle

Eukaryotic Cells
By the end of this section, you will be able to:

- Describe the structure of eukaryotic cells
- Compare animal cells with plant cells
- State the role of the plasma membrane
- Summarize the functions of the major cell organelles

Have you ever heard the phrase "form follows function?" It's a philosophy practiced in many industries. In architecture, this means that buildings should be constructed to support the activities that will be carried out inside them. For example, a skyscraper should be built with several elevator banks; a hospital should be built so that its emergency room is easily accessible.

Our natural world also utilizes the principle of form following function, especially in cell biology, and this will become clear as we explore eukaryotic cells ([link]). Unlike prokaryotic cells, **eukaryotic cells** have: 1) a membrane-bound nucleus; 2) numerous membrane-bound **organelles** such as the endoplasmic reticulum, Golgi apparatus, chloroplasts, mitochondria, and others; and 3) several, rod-shaped chromosomes. Because a eukaryotic cell's nucleus is surrounded by a membrane, it is often said to have a "true nucleus." The word "organelle" means "little organ," and, as already mentioned, organelles have specialized cellular functions, just as the organs of your body have specialized functions.

At this point, it should be clear to you that eukaryotic cells have a more complex structure than prokaryotic cells. Organelles allow different functions to be compartmentalized in different areas of the cell. Before turning to organelles, let's first examine two important components of the cell: the plasma membrane and the cytoplasm.

Note:
Art Connection

These figures show the major organelles and other cell components of (a) a typical animal cell and (b) a typical eukaryotic plant cell. The plant cell has a cell wall, chloroplasts, plastids, and a central vacuole —structures not found in animal cells. Plant cells do not have lysosomes or centrosomes.
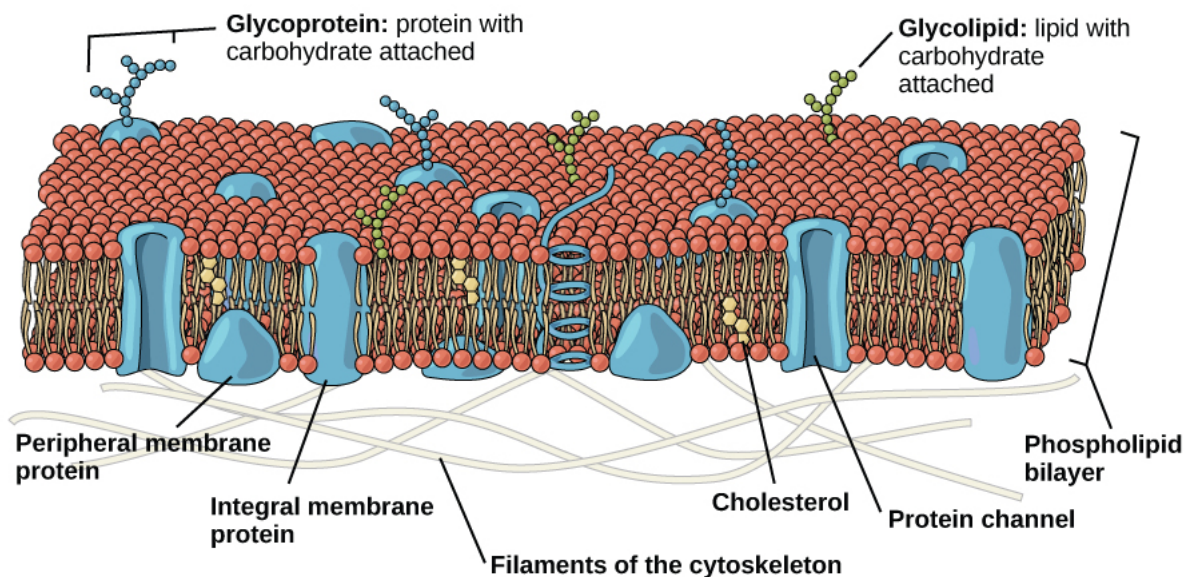
Nucleus
Nuclear envelope: membrane enclosing the nucleus. Protein-lined pores allow material to move in and out.
Chromatin: DNA plus associated proteins.
Nucleolus: condensed region where ribosomes are formed.

Peroxisome: metabolizes waste

Endoplasmic reticulum
Rough: associated with ribosomes; makes secretory and membrane proteins.
Smooth: makes lipids.

Cytoskeleton
Microtubules: form the mitotic spindle and maintain cell shape.
Centrosome: microtubule-organizing center.
Intermediate filaments: fibrous proteins that hold organelles in place.
Microfilaments: fibrous proteins; form the cellular cortex.

Plasma membrane
Lysosome: digests food and waste materials.
Golgi apparatus: modifies proteins.
Cytoplasm
Mitochondria: produce energy.
Vacuole

Plasmodesmata channels connect two plant cells
Cell wall maintains cell shape
Plasma membrane
Cytoplasm
Central Vacuole filled with cell sap that maintains pressure against cell wall
Cytoskeleton microtubules intermediate filaments microfilaments

Endoplasmic Reticulum smooth rough

Nucleus contains chromatin, a nuclear envelope, and a nucleolus, as in an animal cell

Ribosomes
Golgi apparatus
Mitochondria
Peroxisome

Chloroplast site of photosynthesis
Plastid store pigments

If the nucleolus were not able to carry out its function, what other cellular organelles would be affected?
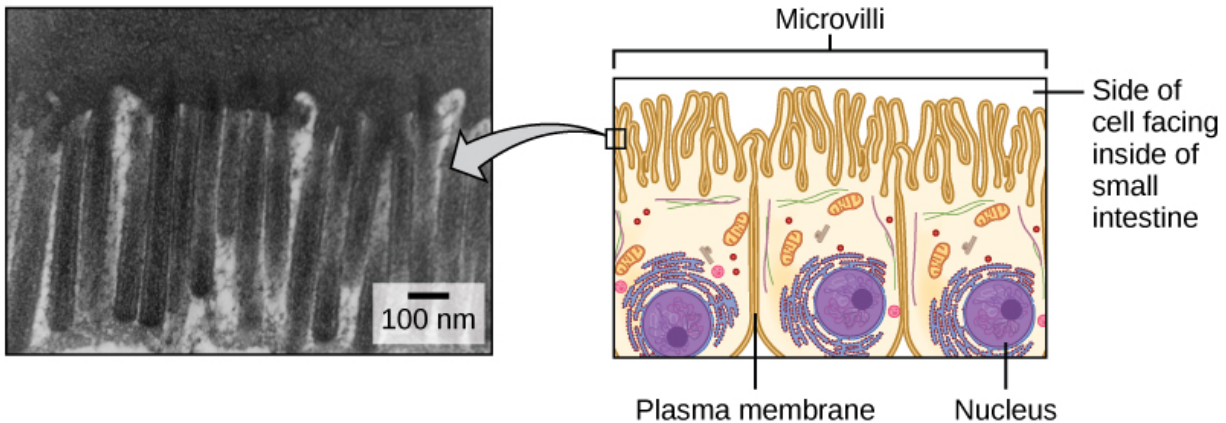
The Plasma Membrane

Like prokaryotes, eukaryotic cells have a **plasma membrane** ([link]), a phospholipid bilayer with embedded proteins that separates the internal contents of the cell from its surrounding environment. A phospholipid is a lipid molecule with two fatty acid chains and a phosphate-containing group. The plasma membrane controls the passage of organic molecules, ions, water, and oxygen into and out of the cell. Wastes (such as carbon dioxide and ammonia) also leave the cell by passing through the plasma membrane.

Glycoprotein: protein with carbohydrate attached

Glycolipid: lipid with carbohydrate attached

Peripheral membrane protein

Integral membrane protein

Filaments of the cytoskeleton

Cholesterol

Protein channel

Phospholipid bilayer

The eukaryotic plasma membrane is a phospholipid bilayer with proteins and cholesterol embedded in it.

The plasma membranes of cells that specialize in absorption are folded into fingerlike projections called microvilli (singular = microvillus); ([link]). Such cells are typically found lining the small intestine, the organ that absorbs nutrients from digested food. This is an excellent example of form following function. People with celiac disease have an immune response to gluten, which is a protein found in wheat, barley, and rye. The immune response damages microvilli, and thus, afflicted individuals cannot absorb

nutrients. This leads to malnutrition, cramping, and diarrhea. Patients suffering from celiac disease must follow a gluten-free diet.


Microvilli, shown here as they appear on cells lining the small intestine, increase the surface area available for absorption. These microvilli are only found on the area of the plasma membrane that faces the cavity from which substances will be absorbed. (credit "micrograph": modification of work by Louisa Howard)

The Cytoplasm

The **cytoplasm** is the entire region of a cell between the plasma membrane and the nuclear envelope (a structure to be discussed shortly). It is made up of organelles suspended in the gel-like **cytosol**, the cytoskeleton, and various chemicals ([link]). Even though the cytoplasm consists of 70 to 80 percent water, it has a semi-solid consistency, which comes from the proteins within it. However, proteins are not the only organic molecules found in the cytoplasm. Glucose and other simple sugars, polysaccharides, amino acids, nucleic acids, fatty acids, and derivatives of glycerol are found there, too. Ions of sodium, potassium, calcium, and many other elements are also dissolved in the cytoplasm. Many metabolic reactions, including protein synthesis, take place in the cytoplasm.

The Nucleus

Typically, the nucleus is the most prominent organelle in a cell ([link]). The **nucleus** (plural = nuclei) houses the cell's DNA and directs the synthesis of ribosomes and proteins. Let's look at it in more detail ([link]).
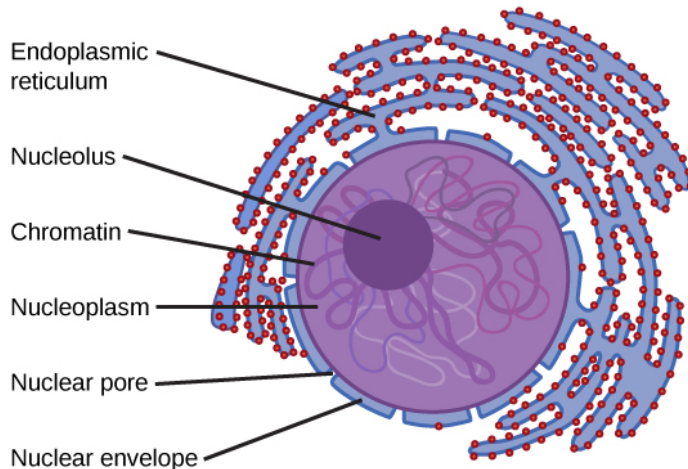
The nucleus stores chromatin (DNA plus proteins) in a gel-like substance called the nucleoplasm. The nucleolus is a condensed region of chromatin where ribosome synthesis occurs. The boundary of the nucleus is called the nuclear envelope. It consists of two phospholipid bilayers: an outer membrane and an inner membrane. The nuclear membrane is continuous with the endoplasmic reticulum. Nuclear pores allow substances to enter and exit the nucleus.

The Nuclear Envelope

The **nuclear envelope** is a double-membrane structure that constitutes the outermost portion of the nucleus ([link]). Both the inner and outer membranes of the nuclear envelope are phospholipid bilayers.

The nuclear envelope is punctuated with pores that control the passage of ions, molecules, and RNA between the nucleoplasm and cytoplasm. The **nucleoplasm** is the semi-solid fluid inside the nucleus, where we find the chromatin and the nucleolus.

Chromatin and Chromosomes

To understand chromatin, it is helpful to first consider chromosomes. **Chromosomes** are structures within the nucleus that are made up of DNA, the hereditary material. You may remember that in prokaryotes, DNA is organized into a single circular chromosome. In eukaryotes, chromosomes are linear structures. Every eukaryotic species has a specific number of chromosomes in the nuclei of its body's cells. For example, in humans, the chromosome number is 46, while in fruit flies, it is eight. Chromosomes are only visible and distinguishable from one another when the cell is getting ready to divide. When the cell is in the growth and maintenance phases of its life cycle, proteins are attached to chromosomes, and they resemble an unwound, jumbled bunch of threads. These unwound protein-chromosome complexes are called **chromatin** ([link]); chromatin describes the material that makes up the chromosomes both when condensed and decondensed.
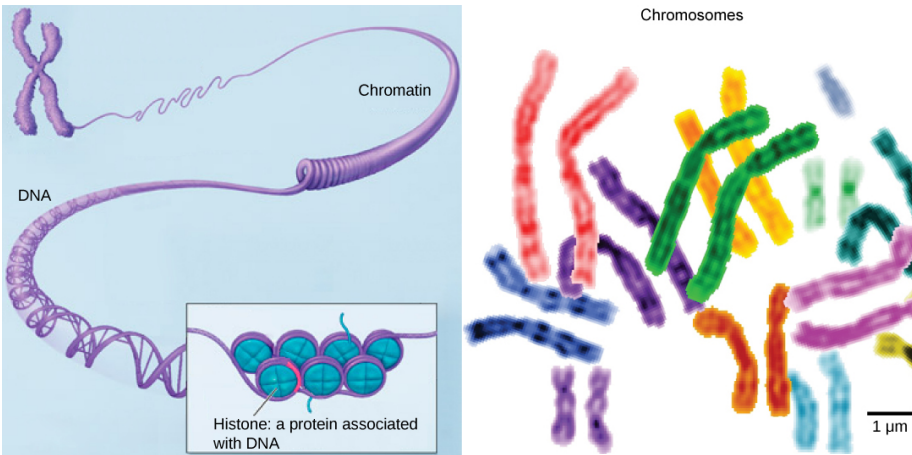
(a) This image shows various levels of the organization of chromatin (DNA and protein). (b) This image shows paired chromosomes. (credit b: modification of work by NIH; scale-bar data from Matt Russell)

The Nucleolus

We already know that the nucleus directs the synthesis of ribosomes, but how does it do this? Some chromosomes have sections of DNA that encode ribosomal RNA. A darkly staining area within the nucleus called the **nucleolus** (plural = nucleoli) aggregates the ribosomal RNA with associated proteins to assemble the ribosomal subunits that are then transported out through the pores in the nuclear envelope to the cytoplasm.

Ribosomes

Ribosomes are the cellular structures responsible for protein synthesis. When viewed through an electron microscope, ribosomes appear either as clusters (polyribosomes) or single, tiny dots that float freely in the cytoplasm. They may be attached to the cytoplasmic side of the plasma membrane or the cytoplasmic side of the endoplasmic reticulum and the

outer membrane of the nuclear envelope ([link]). Electron microscopy has shown us that ribosomes, which are large complexes of protein and RNA, consist of two subunits, aptly called large and small ([link]). Ribosomes receive their "orders" for protein synthesis from the nucleus where the DNA is transcribed into messenger RNA (mRNA). The mRNA travels to the ribosomes, which translate the code provided by the sequence of the nitrogenous bases in the mRNA into a specific order of amino acids in a protein. Amino acids are the building blocks of proteins.
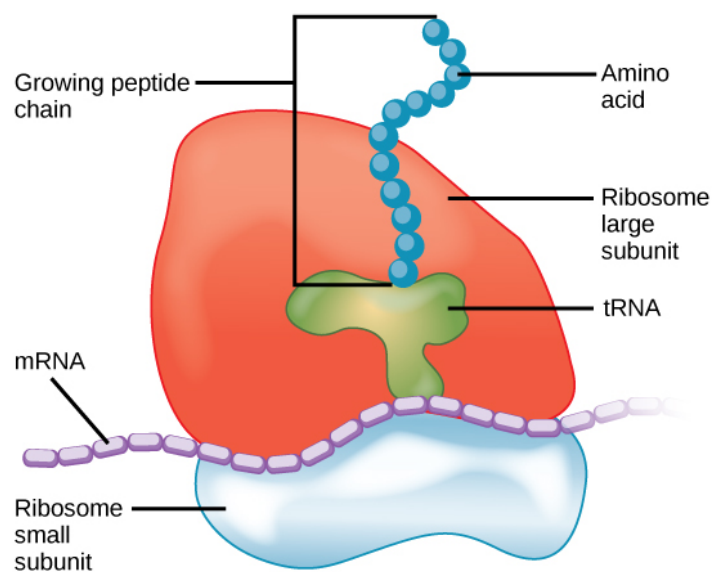
Ribosomes are made up of a large subunit (top) and a small subunit (bottom). During protein synthesis, ribosomes assemble amino acids into proteins.

Because proteins synthesis is an essential function of all cells (including enzymes, hormones, antibodies, pigments, structural components, and surface receptors), ribosomes are found in practically every cell. Ribosomes are particularly abundant in cells that synthesize large amounts of protein. For example, the pancreas is responsible for creating several digestive

enzymes and the cells that produce these enzymes contain many ribosomes. Thus, we see another example of form following function.

Mitochondria

Mitochondria (singular = mitochondrion) are often called the "powerhouses" or "energy factories" of a cell because they are responsible for making adenosine triphosphate (ATP), the cell's main energy-carrying molecule. ATP represents the short-term stored energy of the cell. Cellular respiration is the process of making ATP using the chemical energy found in glucose and other nutrients. In mitochondria, this process uses oxygen and produces carbon dioxide as a waste product. In fact, the carbon dioxide that you exhale with every breath comes from the cellular reactions that produce carbon dioxide as a byproduct.

In keeping with our theme of form following function, it is important to point out that muscle cells have a very high concentration of mitochondria that produce ATP. Your muscle cells need a lot of energy to keep your body moving. When your cells don't get enough oxygen, they do not make a lot of ATP. Instead, the small amount of ATP they make in the absence of oxygen is accompanied by the production of lactic acid.

Mitochondria are oval-shaped, double membrane organelles ([link]) that have their own ribosomes and DNA. Each membrane is a phospholipid bilayer embedded with proteins. The inner layer has folds called cristae. The area surrounded by the folds is called the mitochondrial matrix. The cristae and the matrix have different roles in cellular respiration.
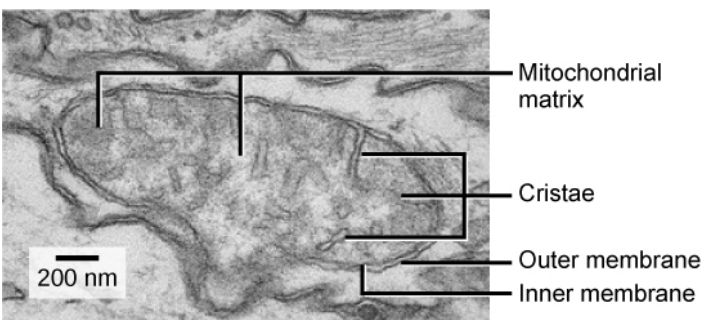
This electron micrograph shows a mitochondrion as viewed with a transmission electron microscope. This organelle has an outer membrane and an inner membrane. The inner membrane contains folds, called cristae, which increase its surface area. The space between the two membranes is called the intermembrane space, and the space inside the inner membrane is called the mitochondrial matrix. ATP synthesis takes place on the inner membrane. (credit: modification of work by Matthew Britton; scale-bar data from Matt Russell)

Peroxisomes

Peroxisomes are small, round organelles enclosed by single membranes. They carry out oxidation reactions that break down fatty acids and amino acids. They also detoxify many poisons that may enter the body. (Many of these oxidation reactions release hydrogen peroxide, H_2O_2, which would be damaging to cells; however, when these reactions are confined to peroxisomes, enzymes safely break down the H_2O_2 into oxygen and water.) For example, alcohol is detoxified by peroxisomes in liver cells. Glyoxysomes, which are specialized peroxisomes in plants, are responsible for converting stored fats into sugars.

Vesicles and Vacuoles

Vesicles and **vacuoles** are membrane-bound sacs that function in storage and transport. Other than the fact that vacuoles are somewhat larger than vesicles, there is a very subtle distinction between them: The membranes of

vesicles can fuse with either the plasma membrane or other membrane systems within the cell. Additionally, some agents such as enzymes within plant vacuoles break down macromolecules. The membrane of a vacuole does not fuse with the membranes of other cellular components.

Animal Cells versus Plant Cells

At this point, you know that each eukaryotic cell has a plasma membrane, cytoplasm, a nucleus, ribosomes, mitochondria, peroxisomes, and in some, vacuoles, but there are some striking differences between animal and plant cells. While both animal and plant cells have microtubule organizing centers (MTOCs), animal cells also have centrioles associated with the MTOC: a complex called the centrosome. Animal cells each have a centrosome and lysosomes, whereas plant cells do not. Plant cells have a cell wall, chloroplasts and other specialized plastids, and a large central vacuole, whereas animal cells do not.

The Centrosome

The **centrosome** is a microtubule-organizing center found near the nuclei of animal cells. It contains a pair of centrioles, two structures that lie perpendicular to each other ([link]). Each centriole is a cylinder of nine triplets of microtubules.
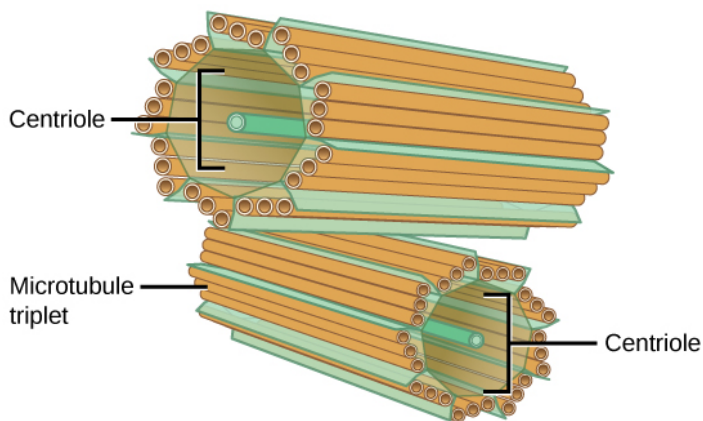
The centrosome consists of two centrioles that lie at right angles to each other. Each centriole is a cylinder made up of nine triplets of microtubules. Nontubulin proteins (indicated by the green lines) hold the microtubule triplets together.

The centrosome (the organelle where all microtubules originate) replicates itself before a cell divides, and the centrioles appear to have some role in pulling the duplicated chromosomes to opposite ends of the dividing cell. However, the exact function of the centrioles in cell division isn't clear, because cells that have had the centrosome removed can still divide, and plant cells, which lack centrosomes, are capable of cell division.

Lysosomes

Animal cells have another set of organelles not found in plant cells: lysosomes. The **lysosomes** are the cell's "garbage disposal." In plant cells, the digestive processes take place in vacuoles. Enzymes within the lysosomes aid the breakdown of proteins, polysaccharides, lipids, nucleic acids, and even worn-out organelles. These enzymes are active at a much lower pH than that of the cytoplasm. Therefore, the pH within lysosomes is more acidic than the pH of the cytoplasm. Many reactions that take place in the cytoplasm could not occur at a low pH, so again, the advantage of compartmentalizing the eukaryotic cell into organelles is apparent.

The Cell Wall

If you examine [link]**b**, the diagram of a plant cell, you will see a structure external to the plasma membrane called the cell wall. The **cell wall** is a rigid covering that protects the cell, provides structural support, and gives

shape to the cell. Fungal and protistan cells also have cell walls. While the chief component of prokaryotic cell walls is peptidoglycan, the major organic molecule in the plant cell wall is cellulose ([link]), a polysaccharide made up of glucose units. Have you ever noticed that when you bite into a raw vegetable, like celery, it crunches? That's because you are tearing the rigid cell walls of the celery cells with your teeth.
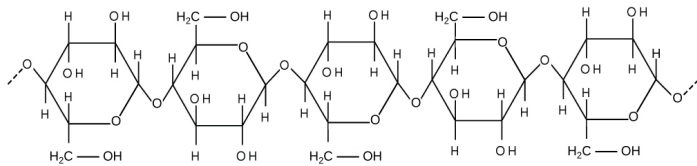
Cellulose is a long chain of β-glucose molecules connected by a 1-4 linkage. The dashed lines at each end of the figure indicate a series of many more glucose units. The size of the page makes it impossible to portray an entire cellulose molecule.

Chloroplasts

Like the mitochondria, chloroplasts have their own DNA and ribosomes, but chloroplasts have an entirely different function. **Chloroplasts** are plant cell organelles that carry out photosynthesis. Photosynthesis is the series of reactions that use carbon dioxide, water, and light energy to make glucose and oxygen. This is a major difference between plants and animals; plants (autotrophs) are able to make their own food, like sugars, while animals (heterotrophs) must ingest their food.

Like mitochondria, chloroplasts have outer and inner membranes, but within the space enclosed by a chloroplast's inner membrane is a set of

interconnected and stacked fluid-filled membrane sacs called thylakoids ([link]). Each stack of thylakoids is called a granum (plural = grana). The fluid enclosed by the inner membrane that surrounds the grana is called the stroma.
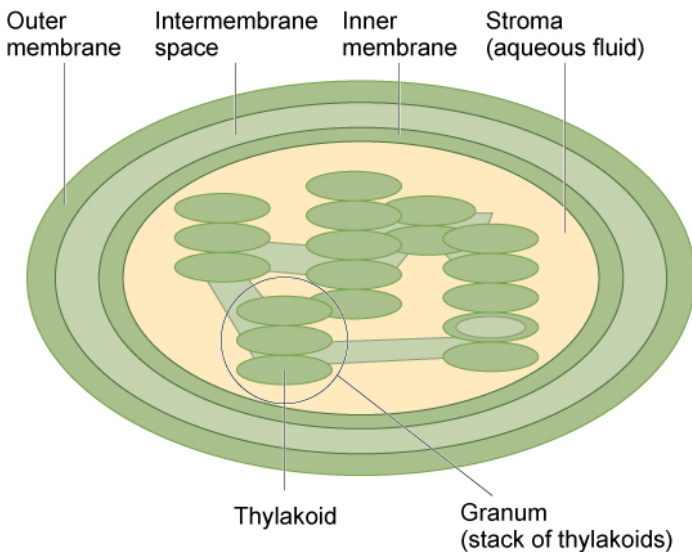
The chloroplast has an outer membrane, an inner membrane, and membrane structures called thylakoids that are stacked into grana. The space inside the thylakoid membranes is called the thylakoid space. The light harvesting reactions take place in the thylakoid membranes, and the synthesis of sugar takes place in the fluid inside the inner membrane, which is called the stroma. Chloroplasts also have their own genome, which is contained on a single circular chromosome.

The chloroplasts contain a green pigment called **chlorophyll**, which captures the light energy that drives the reactions of photosynthesis. Like plant cells, photosynthetic protists also have chloroplasts. Some bacteria perform photosynthesis, but their chlorophyll is not relegated to an organelle.

Note:
Evolution Connection
Endosymbiosis
We have mentioned that both mitochondria and chloroplasts contain DNA and ribosomes. Have you wondered why? Strong evidence points to endosymbiosis as the explanation.
Symbiosis is a relationship in which organisms from two separate species depend on each other for their survival. Endosymbiosis (endo- = "within") is a mutually beneficial relationship in which one organism lives inside the other. Endosymbiotic relationships abound in nature. We have already mentioned that microbes that produce vitamin K live inside the human gut. This relationship is beneficial for us because we are unable to synthesize vitamin K. It is also beneficial for the microbes because they are protected from other organisms and from drying out, and they receive abundant food from the environment of the large intestine.
Scientists have long noticed that bacteria, mitochondria, and chloroplasts are similar in size. We also know that bacteria have DNA and ribosomes, just as mitochondria and chloroplasts do. Scientists believe that host cells and bacteria formed an endosymbiotic relationship when the host cells ingested both aerobic and autotrophic bacteria (cyanobacteria) but did not destroy them. Through many millions of years of evolution, these ingested bacteria became more specialized in their functions, with the aerobic bacteria becoming mitochondria and the autotrophic bacteria becoming chloroplasts.

The Central Vacuole

Previously, we mentioned vacuoles as essential components of plant cells. If you look at [link]**b**, you will see that plant cells each have a large central vacuole that occupies most of the area of the cell. The **central vacuole** plays a key role in regulating the cell's concentration of water in changing environmental conditions. Have you ever noticed that if you forget to water a plant for a few days, it wilts? That's because as the water concentration in the soil becomes lower than the water concentration in the plant, water moves out of the central vacuoles and cytoplasm. As the central vacuole shrinks, it leaves the cell wall unsupported. This loss of support to the cell walls of plant cells results in the wilted appearance of the plant.

The central vacuole also supports the expansion of the cell. When the central vacuole holds more water, the cell gets larger without having to invest a lot of energy in synthesizing new cytoplasm.

Section Summary

Like a prokaryotic cell, a eukaryotic cell has a plasma membrane, cytoplasm, and ribosomes, but a eukaryotic cell is typically larger than a prokaryotic cell, has a true nucleus (meaning its DNA is surrounded by a membrane), and has other membrane-bound organelles that allow for compartmentalization of functions. The plasma membrane is a phospholipid bilayer embedded with proteins. The nucleus's nucleolus is the site of ribosome assembly. Ribosomes are either found in the cytoplasm or attached to the cytoplasmic side of the plasma membrane or endoplasmic reticulum. They perform protein synthesis. Mitochondria participate in cellular respiration; they are responsible for the majority of ATP produced in the cell. Peroxisomes hydrolyze fatty acids, amino acids, and some toxins. Vesicles and vacuoles are storage and transport compartments. In plant cells, vacuoles also help break down macromolecules.

Animal cells also have a centrosome and lysosomes. The centrosome has two bodies perpendicular to each other, the centrioles, and has an unknown purpose in cell division. Lysosomes are the digestive organelles of animal cells.

Plant cells and plant-like cells each have a cell wall, chloroplasts, and a central vacuole. The plant cell wall, whose primary component is cellulose, protects the cell, provides structural support, and gives shape to the cell. Photosynthesis takes place in chloroplasts. The central vacuole can expand without having to produce more cytoplasm.

Art Connections

Exercise:

Problem:

[link] If the nucleolus were not able to carry out its function, what other cellular organelles would be affected?

Solution:

[link] Free ribosomes and rough endoplasmic reticulum (which contains ribosomes) would not be able to form.

Review Questions

Exercise:

Problem:

Which of the following is surrounded by two phospholipid bilayers?

   a. the ribosomes
   b. the vesicles
   c. the cytoplasm
   d. the nucleoplasm

Solution:

D

Exercise:

Problem: Peroxisomes got their name because hydrogen peroxide is:

    a. used in their detoxification reactions
    b. produced during their oxidation reactions
    c. incorporated into their membranes
    d. a cofactor for the organelles' enzymes

Solution:

B

Exercise:

Problem:

In plant cells, the function of the lysosomes is carried out by
_____.

    a. vacuoles
    b. peroxisomes
    c. ribosomes
    d. nuclei

Solution:

A

Exercise:

Problem:

Which of the following is found both in eukaryotic and prokaryotic cells?

    a. nucleus
    b. mitochondrion

c. vacuole

d. ribosomes

Solution:

D

Free Response

Exercise:

Problem:

You already know that ribosomes are abundant in red blood cells. In what other cells of the body would you find them in great abundance? Why?

Solution:

Ribosomes are abundant in muscle cells as well because muscle cells are constructed of the proteins made by the ribosomes.

Exercise:

Problem:

What are the structural and functional similarities and differences between mitochondria and chloroplasts?

Solution:

Both are similar in that they are enveloped in a double membrane, both have an intermembrane space, and both make ATP. Both mitochondria and chloroplasts have DNA, and mitochondria have inner folds called cristae and a matrix, while chloroplasts have chlorophyll and accessory pigments in the thylakoids that form stacks (grana) and a stroma.

Glossary

cell wall
    rigid cell covering made of various molecules that protects the cell, provides structural support, and gives shape to the cell

central vacuole
    large plant cell organelle that regulates the cell's storage compartment, holds water, and plays a significant role in cell growth as the site of macromolecule degradation

centrosome
    region in animal cells made of two centrioles

chlorophyll
    green pigment that captures the light energy that drives the light reactions of photosynthesis

chloroplast
    plant cell organelle that carries out photosynthesis

chromatin
    protein-DNA complex that serves as the building material of chromosomes

chromosome
    structure within the nucleus that is made up of chromatin that contains DNA, the hereditary material

cytoplasm
    entire region between the plasma membrane and the nuclear envelope, consisting of organelles suspended in the gel-like cytosol, the cytoskeleton, and various chemicals

cytosol
    gel-like material of the cytoplasm in which cell structures are suspended

eukaryotic cell
    cell that has a membrane-bound nucleus and several other membrane-
    bound compartments or sacs

lysosome
    organelle in an animal cell that functions as the cell's digestive
    component; it breaks down proteins, polysaccharides, lipids, nucleic
    acids, and even worn-out organelles

mitochondria
    (singular = mitochondrion) cellular organelles responsible for carrying
    out cellular respiration, resulting in the production of ATP, the cell's
    main energy-carrying molecule

nuclear envelope
    double-membrane structure that constitutes the outermost portion of
    the nucleus

nucleolus
    darkly staining body within the nucleus that is responsible for
    assembling the subunits of the ribosomes

nucleoplasm
    semi-solid fluid inside the nucleus that contains the chromatin and
    nucleolus

nucleus
    cell organelle that houses the cell's DNA and directs the synthesis of
    ribosomes and proteins

organelle
    compartment or sac within a cell

peroxisome
    small, round organelle that contains hydrogen peroxide, oxidizes fatty
    acids and amino acids, and detoxifies many poisons

plasma membrane

phospholipid bilayer with embedded (integral) or attached (peripheral) proteins, and separates the internal content of the cell from its surrounding environment

ribosome
cellular structure that carries out protein synthesis

vacuole
membrane-bound sac, somewhat larger than a vesicle, which functions in cellular storage and transport

vesicle
small, membrane-bound sac that functions in cellular storage and transport; its membrane is capable of fusing with the plasma membrane and the membranes of the endoplasmic reticulum and Golgi apparatus

The Endomembrane System and Proteins
By the end of this section, you will be able to:

- List the components of the endomembrane system
- Recognize the relationship between the endomembrane system and its functions

The endomembrane system (endo = "within") is a group of membranes and organelles ([link]) in eukaryotic cells that works together to modify, package, and transport lipids and proteins. It includes the nuclear envelope, lysosomes, and vesicles, which we've already mentioned, and the endoplasmic reticulum and Golgi apparatus, which we will cover shortly. Although not technically *within* the cell, the plasma membrane is included in the endomembrane system because, as you will see, it interacts with the other endomembranous organelles. The endomembrane system does not include the membranes of either mitochondria or chloroplasts.

Note:
Art Connection

Nucleus

Rough ER

cis face

Cisternae

trans face

Golgi Apparatus

Transport vesicle
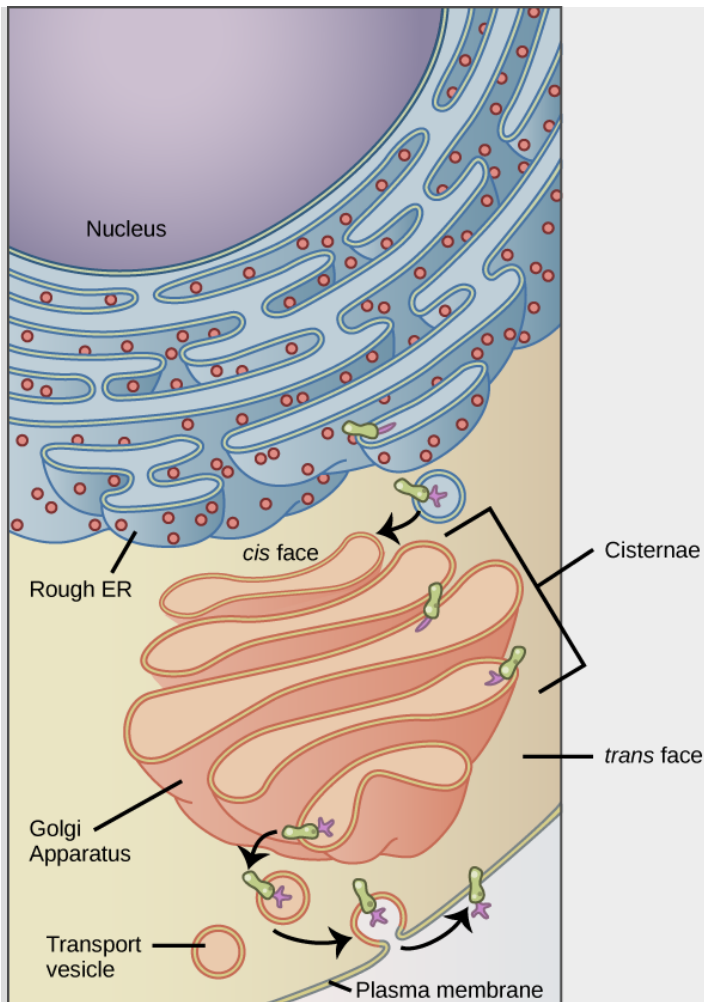
Plasma membrane

"Membrane and secretory proteins are synthesized in the rough endoplasmic reticulum (RER). The RER also sometimes modifies proteins. In this illustration, a (green) integral membrane protein in the ER is modified by attachment of a (purple) carbohydrate. Vesicles with the integral protein bud from the ER and fuse with the cis face of the Golgi apparatus. As the protein passes along the Golgi's cisternae, it is further modified by the addition of more carbohydrates. After its synthesis is

complete, it exits as integral membrane protein of the vesicle that bud from the Golgi's **trans** face and when the vesicle fuses with the cell membrane the protein becomes integral portion of that cell membrane. (credit: modification of work by Magnus Manske)

If a peripheral membrane protein were synthesized in the lumen (inside) of the ER, would it end up on the inside or outside of the plasma membrane?
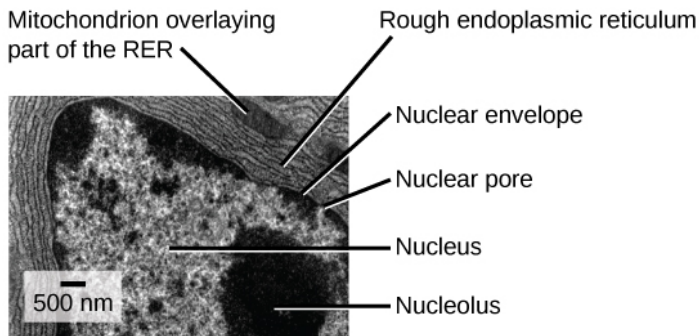
The Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** ([link]) is a series of interconnected membranous sacs and tubules that collectively modifies proteins and synthesizes lipids. However, these two functions are performed in separate areas of the ER: the rough ER and the smooth ER, respectively.

The hollow portion of the ER tubules is called the lumen or cisternal space. The membrane of the ER, which is a phospholipid bilayer embedded with proteins, is continuous with the nuclear envelope.

Rough ER

The **rough endoplasmic reticulum (RER)** is so named because the ribosomes attached to its cytoplasmic surface give it a studded appearance when viewed through an electron microscope ([link]).

This transmission electron micrograph shows the rough endoplasmic reticulum and other organelles in a pancreatic cell. (credit: modification of work by Louisa Howard)

Ribosomes transfer their newly synthesized proteins into the lumen of the RER where they undergo structural modifications, such as folding or the acquisition of side chains. These modified proteins will be incorporated into cellular membranes—the membrane of the ER or those of other organelles—or secreted from the cell (such as protein hormones, enzymes). The RER also makes phospholipids for cellular membranes.

If the phospholipids or modified proteins are not destined to stay in the RER, they will reach their destinations via transport vesicles that bud from the RER's membrane ([link]).

Since the RER is engaged in modifying proteins (such as enzymes, for example) that will be secreted from the cell, you would be correct in assuming that the RER is abundant in cells that secrete proteins. This is the case with cells of the liver, for example.

Smooth ER

The **smooth endoplasmic reticulum (SER)** is continuous with the RER but has few or no ribosomes on its cytoplasmic surface ([link]). Functions

of the SER include synthesis of carbohydrates, lipids, and steroid hormones; detoxification of medications and poisons; and storage of calcium ions.

In muscle cells, a specialized SER called the sarcoplasmic reticulum is responsible for storage of the calcium ions that are needed to trigger the coordinated contractions of the muscle cells.

Note:
Career Connection
Cardiologist
Heart disease is the leading cause of death in the United States. This is primarily due to our sedentary lifestyle and our high trans-fat diets.
Heart failure is just one of many disabling heart conditions. Heart failure does not mean that the heart has stopped working. Rather, it means that the heart can't pump with sufficient force to transport oxygenated blood to all the vital organs. Left untreated, heart failure can lead to kidney failure and failure of other organs.
The wall of the heart is composed of cardiac muscle tissue. Heart failure occurs when the endoplasmic reticula of cardiac muscle cells do not

function properly. As a result, an insufficient number of calcium ions are available to trigger a sufficient contractile force.

Cardiologists (cardi- = "heart"; -ologist = "one who studies") are doctors who specialize in treating heart diseases, including heart failure. Cardiologists can make a diagnosis of heart failure via physical examination, results from an electrocardiogram (ECG, a test that measures the electrical activity of the heart), a chest X-ray to see whether the heart is enlarged, and other tests. If heart failure is diagnosed, the cardiologist will typically prescribe appropriate medications and recommend a reduction in table salt intake and a supervised exercise program.

The Golgi Apparatus

We have already mentioned that vesicles can bud from the ER and transport their contents elsewhere, but where do the vesicles go? Before reaching their final destination, the lipids or proteins within the transport vesicles still need to be sorted, packaged, and tagged so that they wind up in the right place. Sorting, tagging, packaging, and distribution of lipids and proteins takes place in the **Golgi apparatus** (also called the Golgi body), a series of flattened membranes ([link]).

Golgi apparatus

100 nm
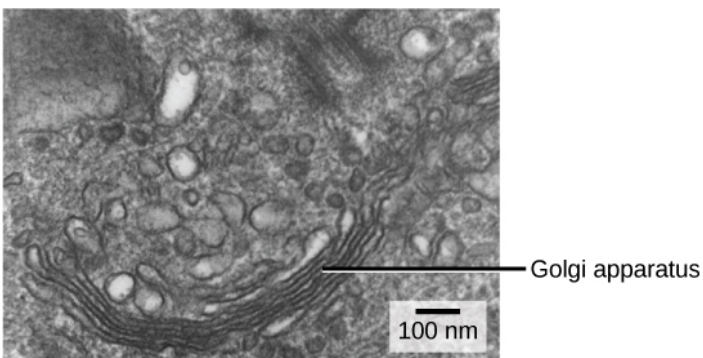
The Golgi apparatus in this white blood cell is visible as a stack of semicircular, flattened rings in the lower portion of the image. Several

vesicles can be seen near the Golgi apparatus. (credit: modification of work by Louisa Howard)

The receiving side of the Golgi apparatus is called the *cis* face. The opposite side is called the *trans* face. The transport vesicles that formed from the ER travel to the *cis* face, fuse with it, and empty their contents into the lumen of the Golgi apparatus. As the proteins and lipids travel through the Golgi, they undergo further modifications that allow them to be sorted. The most frequent modification is the addition of short chains of sugar molecules. These newly modified proteins and lipids are then tagged with phosphate groups or other small molecules so that they can be routed to their proper destinations.

Finally, the modified and tagged proteins are packaged into secretory vesicles that bud from the *trans* face of the Golgi. While some of these vesicles deposit their contents into other parts of the cell where they will be used, other secretory vesicles fuse with the plasma membrane and release their contents outside the cell.

In another example of form following function, cells that engage in a great deal of secretory activity (such as cells of the salivary glands that secrete digestive enzymes or cells of the immune system that secrete antibodies) have an abundance of Golgi.

In plant cells, the Golgi apparatus has the additional role of synthesizing polysaccharides, some of which are incorporated into the cell wall and some of which are used in other parts of the cell.

Note:
Career Connection
Geneticist
Many diseases arise from genetic mutations that prevent the synthesis of critical proteins. One such disease is Lowe disease (also called

oculocerebrorenal syndrome, because it affects the eyes, brain, and kidneys). In Lowe disease, there is a deficiency in an enzyme localized to the Golgi apparatus. Children with Lowe disease are born with cataracts, typically develop kidney disease after the first year of life, and may have impaired mental abilities.

Lowe disease is a genetic disease caused by a mutation on the X chromosome. The X chromosome is one of the two human sex chromosome, as these chromosomes determine a person's sex. Females possess two X chromosomes while males possess one X and one Y chromosome. In females, the genes on only one of the two X chromosomes are expressed. Therefore, females who carry the Lowe disease gene on one of their X chromosomes have a 50/50 chance of having the disease. However, males only have one X chromosome and the genes on this chromosome are always expressed. Therefore, males will always have Lowe disease if their X chromosome carries the Lowe disease gene. The location of the mutated gene, as well as the locations of many other mutations that cause genetic diseases, has now been identified. Through prenatal testing, a woman can find out if the fetus she is carrying may be afflicted with one of several genetic diseases.
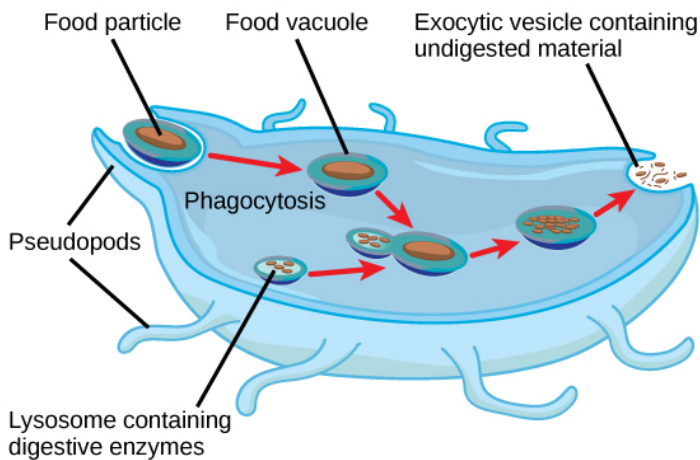
Geneticists analyze the results of prenatal genetic tests and may counsel pregnant women on available options. They may also conduct genetic research that leads to new drugs or foods, or perform DNA analyses that are used in forensic investigations.

Lysosomes

In addition to their role as the digestive component and organelle-recycling facility of animal cells, lysosomes are considered to be parts of the endomembrane system. Lysosomes also use their hydrolytic enzymes to destroy pathogens (disease-causing organisms) that might enter the cell. A good example of this occurs in a group of white blood cells called macrophages, which are part of your body's immune system. In a process known as phagocytosis or endocytosis, a section of the plasma membrane of the macrophage invaginates (folds in) and engulfs a pathogen. The invaginated section, with the pathogen inside, then pinches itself off from

the plasma membrane and becomes a vesicle. The vesicle fuses with a lysosome. The lysosome's hydrolytic enzymes then destroy the pathogen ([link]).

Phagocytosis

Food particle   Food vacuole   Exocytic vesicle containing undigested material

Phagocytosis

Pseudopods

Lysosome containing digestive enzymes

A macrophage has engulfed (phagocytized) a potentially pathogenic bacterium and then fuses with a lysosomes within the cell to destroy the pathogen. Other organelles are present in the cell but for simplicity are not shown.

Section Summary

The endomembrane system includes the nuclear envelope, lysosomes, vesicles, the ER, and Golgi apparatus, as well as the plasma membrane. These cellular components work together to modify, package, tag, and transport proteins and lipids that form the membranes.

The RER modifies proteins and synthesizes phospholipids used in cell membranes. The SER synthesizes carbohydrates, lipids, and steroid

hormones; engages in the detoxification of medications and poisons; and stores calcium ions. Sorting, tagging, packaging, and distribution of lipids and proteins take place in the Golgi apparatus. Lysosomes are created by the budding of the membranes of the RER and Golgi. Lysosomes digest macromolecules, recycle worn-out organelles, and destroy pathogens.

Art Connections

Exercise:

Problem:

[link] If a peripheral membrane protein were synthesized in the lumen (inside) of the ER, would it end up on the inside or outside of the plasma membrane?

Solution:

[link] It would end up on the outside. After the vesicle passes through the Golgi apparatus and fuses with the plasma membrane, it turns inside out.

Review Questions

Exercise:

Problem:

Which of the following is not a component of the endomembrane system?

    a. mitochondrion
    b. Golgi apparatus
    c. endoplasmic reticulum
    d. lysosome

Solution:

A

Exercise:

Problem:

The process by which a cell engulfs a foreign particle is known as:

  a. endosymbiosis
  b. phagocytosis
  c. hydrolysis
  d. membrane synthesis

Solution:

B

Exercise:

Problem:

Which of the following is most likely to have the greatest concentration of smooth endoplasmic reticulum?

  a. a cell that secretes enzymes
  b. a cell that destroys pathogens
  c. a cell that makes steroid hormones
  d. a cell that engages in photosynthesis

Solution:

C

Exercise:

Problem:

Which of the following sequences correctly lists in order the steps involved in the incorporation of a proteinaceous molecule within a cell?

a. synthesis of the protein on the ribosome; modification in the Golgi apparatus; packaging in the endoplasmic reticulum; tagging in the vesicle

b. synthesis of the protein on the lysosome; tagging in the Golgi; packaging in the vesicle; distribution in the endoplasmic reticulum

c. synthesis of the protein on the ribosome; modification in the endoplasmic reticulum; tagging in the Golgi; distribution via the vesicle

d. synthesis of the protein on the lysosome; packaging in the vesicle; distribution via the Golgi; tagging in the endoplasmic reticulum

---

Solution:

C

Free Response

Exercise:

Problem:

In the context of cell biology, what do we mean by form follows function? What are at least two examples of this concept?

Solution:

"Form follows function" refers to the idea that the function of a body part dictates the form of that body part. As an example, compare your arm to a bat's wing. While the bones of the two correspond, the parts serve different functions in each organism and their forms have adapted to follow that function.

Exercise:

Problem:

In your opinion, is the nuclear membrane part of the endomembrane system? Why or why not? Defend your answer.

Solution:

Since the external surface of the nuclear membrane is continuous with the rough endoplasmic reticulum, which is part of the endomembrane system, then it is correct to say that it is part of the system.

Glossary

endomembrane system
    group of organelles and membranes in eukaryotic cells that work together modifying, packaging, and transporting lipids and proteins

endoplasmic reticulum (ER)
    series of interconnected membranous structures within eukaryotic cells that collectively modify proteins and synthesize lipids

Golgi apparatus
    eukaryotic organelle made up of a series of stacked membranes that sorts, tags, and packages lipids and proteins for distribution

rough endoplasmic reticulum (RER)
    region of the endoplasmic reticulum that is studded with ribosomes and engages in protein modification and phospholipid synthesis

smooth endoplasmic reticulum (SER)
    region of the endoplasmic reticulum that has few or no ribosomes on its cytoplasmic surface and synthesizes carbohydrates, lipids, and steroid hormones; detoxifies certain chemicals (like pesticides, preservatives, medications, and environmental pollutants), and stores calcium ions

The Cytoskeleton
By the end of this section, you will be able to:

- Describe the cytoskeleton
- Compare the roles of microfilaments, intermediate filaments, and microtubules
- Compare and contrast cilia and flagella
- Summarize the differences among the components of prokaryotic cells, animal cells, and plant cells

If you were to remove all the organelles from a cell, would the plasma membrane and the cytoplasm be the only components left? No. Within the cytoplasm, there would still be ions and organic molecules, plus a network of protein fibers that help maintain the shape of the cell, secure some organelles in specific positions, allow cytoplasm and vesicles to move within the cell, and enable cells within multicellular organisms to move. Collectively, this network of protein fibers is known as the **cytoskeleton**. There are three types of fibers within the cytoskeleton: microfilaments, intermediate filaments, and microtubules ([link]). Here, we will examine each.
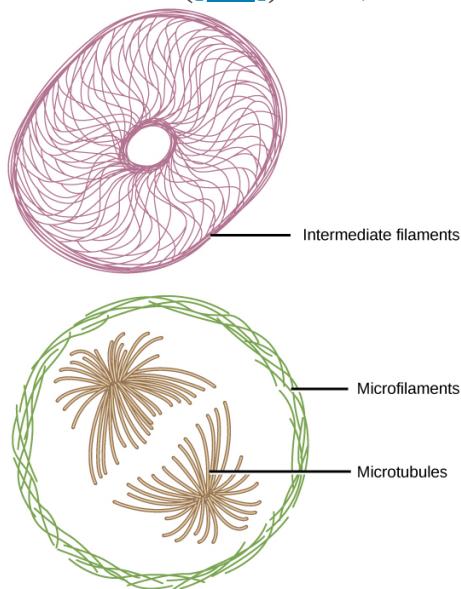

Microfilaments thicken the cortex around the inner edge of a cell; like rubber bands, they resist tension. Microtubules are found in the interior of the cell where they maintain cell shape by resisting compressive forces. Intermediate filaments are found throughout the cell and hold organelles in place.

Microfilaments

Of the three types of protein fibers in the cytoskeleton, **microfilaments** are the narrowest. They function in cellular movement, have a diameter of about 7 nm, and are made of two intertwined strands of a globular protein called actin ([link]). For this reason, microfilaments are also known as actin filaments.
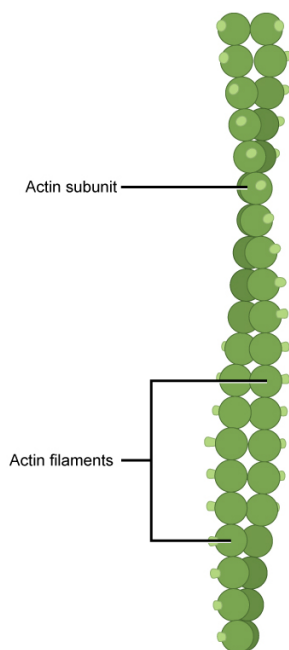
Microfilaments are made of two intertwined strands of actin.

Actin is powered by ATP to assemble its filamentous form, which serves as a track for the movement of a motor protein called myosin. This enables actin to engage in cellular events requiring motion, such as cell division in animal cells and cytoplasmic streaming, which is the circular movement of the cell cytoplasm in plant cells. Actin and myosin are plentiful in muscle cells. When your actin and myosin filaments slide past each other, your muscles contract.

Microfilaments also provide some rigidity and shape to the cell. They can depolymerize (disassemble) and reform quickly, thus enabling a cell to change its shape and move.

White blood cells (your body's infection-fighting cells) make good use of this ability. They can move to the site of an infection and phagocytize the pathogen.

Intermediate Filaments

Intermediate filaments are made of several strands of fibrous proteins that are wound together ([link]). These elements of the cytoskeleton get their name from the fact that their diameter, 8 to 10 nm, is between those of microfilaments and microtubules.

Intermediate filaments consist of several intertwined strands of fibrous proteins.

Intermediate filaments have no role in cell movement. Their function is purely structural. They bear tension, thus maintaining the shape of the cell, and anchor the nucleus and other organelles in place. [link] shows how intermediate filaments create a supportive scaffolding inside the cell.

The intermediate filaments are the most diverse group of cytoskeletal elements. Several types of fibrous proteins are found in the intermediate filaments. You are probably most familiar with keratin, the fibrous protein that strengthens your hair, nails, and the epidermis of the skin.

Microtubules

As their name implies, microtubules are small hollow tubes. The walls of the microtubule are made of polymerized dimers of α-tubulin and β-tubulin, two globular proteins ([link]). With a diameter of about 25 nm, **microtubules** are the widest components of the cytoskeleton. They help the cell resist compression, provide a track along which vesicles move through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. Like microfilaments, microtubules can dissolve and reform quickly.
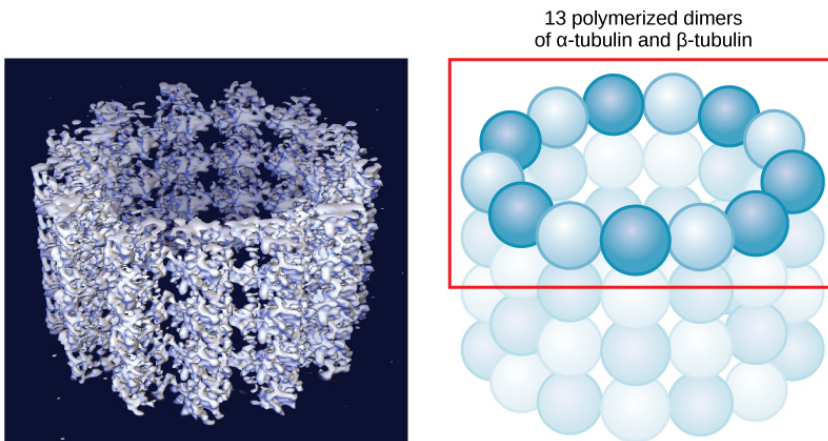
Microtubules are hollow. Their walls consist of 13 polymerized dimers of α-tubulin and β-tubulin (right image). The left image shows the molecular structure of the tube.

Microtubules are also the structural elements of flagella, cilia, and centrioles (the latter are the two perpendicular bodies of the centrosome). In fact, in animal cells, the centrosome is the microtubule-organizing center. In eukaryotic cells, flagella and cilia are quite different structurally from their counterparts in prokaryotes, as discussed below.

Flagella and Cilia

To refresh your memory, **flagella** (singular = flagellum) are long, hair-like structures that extend from the plasma membrane and are used to move an entire cell (for example, sperm, *Euglena*). When present, the cell has just one flagellum or a few flagella. When **cilia** (singular = cilium) are present, however, many of them extend along the entire surface of the plasma membrane. They are short, hair-like structures that are used to move entire cells (such as paramecia) or substances along the outer surface of the cell (for example, the cilia of cells lining the Fallopian tubes that move the ovum toward the uterus, or cilia lining the cells of the respiratory tract that trap particulate matter and move it toward your nostrils.)

Despite their differences in length and number, flagella and cilia share a common structural arrangement of microtubules called a "9 + 2 array." This is an appropriate name because a single flagellum or cilium is made of a ring of nine microtubule doublets, surrounding a single microtubule doublet in the center ([link]).
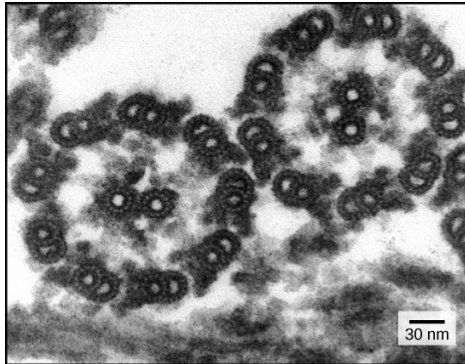
This transmission electron micrograph of two flagella shows the 9 + 2 array of microtubules: nine microtubule doublets surround a single microtubule doublet. (credit: modification of work by Dartmouth Electron Microscope Facility, Dartmouth College; scale-bar data from Matt Russell)

You have now completed a broad survey of the components of prokaryotic and eukaryotic cells. For a summary of cellular components in prokaryotic and eukaryotic cells, see [link].

Components of Prokaryotic and Eukaryotic Cells				
Cell Component	**Function**	**Present in Prokaryotes?**	**Present in Animal Cells?**	**Present in Plant Cells?**
Plasma membrane	Separates cell from external environment; controls passage of organic molecules, ions, water, oxygen, and wastes into and out of cell	Yes	Yes	Yes
Cytoplasm	Provides turgor pressure to plant cells as fluid inside the central vacuole; site of many metabolic reactions; medium in which organelles are found	Yes	Yes	Yes
Nucleolus	Darkened area within the nucleus where ribosomal subunits are synthesized.	No	Yes	Yes
Nucleus	Cell organelle that houses DNA and directs synthesis of ribosomes and proteins	No	Yes	Yes
Ribosomes	Protein synthesis	Yes	Yes	Yes

Components of Prokaryotic and Eukaryotic Cells

Cell Component	Function	Present in Prokaryotes?	Present in Animal Cells?	Present in Plant Cells?
Mitochondria	ATP production/cellular respiration	No	Yes	Yes
Peroxisomes	Oxidizes and thus breaks down fatty acids and amino acids, and detoxifies poisons	No	Yes	Yes
Vesicles and vacuoles	Storage and transport; digestive function in plant cells	No	Yes	Yes
Centrosome	Unspecified role in cell division in animal cells; source of microtubules in animal cells	No	Yes	No
Lysosomes	Digestion of macromolecules; recycling of worn-out organelles	No	Yes	No
Cell wall	Protection, structural support and maintenance of cell shape	Yes, primarily peptidoglycan	No	Yes, primarily cellulose
Chloroplasts	Photosynthesis	No	No	Yes

Components of Prokaryotic and Eukaryotic Cells				
Cell Component	**Function**	**Present in Prokaryotes?**	**Present in Animal Cells?**	**Present in Plant Cells?**
Endoplasmic reticulum	Modifies proteins and synthesizes lipids	No	Yes	Yes
Golgi apparatus	Modifies, sorts, tags, packages, and distributes lipids and proteins	No	Yes	Yes
Cytoskeleton	Maintains cell's shape, secures organelles in specific positions, allows cytoplasm and vesicles to move within cell, and enables unicellular organisms to move independently	Yes	Yes	Yes
Flagella	Cellular locomotion	Some	Some	No, except for some plant sperm cells.
Cilia	Cellular locomotion, movement of particles along extracellular surface of plasma membrane, and filtration	Some	Some	No

Section Summary

The cytoskeleton has three different types of protein elements. From narrowest to widest, they are the microfilaments (actin filaments), intermediate filaments, and microtubules. Microfilaments are often associated with myosin. They provide rigidity and shape to the cell and facilitate cellular movements. Intermediate filaments bear tension and anchor the nucleus and other organelles in place. Microtubules help the cell resist compression, serve as tracks for motor proteins that move vesicles through the cell, and pull replicated chromosomes to opposite ends of a dividing cell. They are also the structural element of centrioles, flagella, and cilia.

Review Questions

Exercise:

  Problem:

  Which of the following have the ability to disassemble and reform quickly?

      a. microfilaments and intermediate filaments
      b. microfilaments and microtubules
      c. intermediate filaments and microtubules
      d. only intermediate filaments

  Solution:

  B

Exercise:

  Problem: Which of the following do not play a role in intracellular movement?

      a. microfilaments and intermediate filaments
      b. microfilaments and microtubules
      c. intermediate filaments and microtubules
      d. only intermediate filaments

  Solution:

  D

Free Response

Exercise:

Problem:

What are the similarities and differences between the structures of centrioles and flagella?

Solution:

Centrioles and flagella are alike in that they are made up of microtubules. In centrioles, two rings of nine microtubule "triplets" are arranged at right angles to one another. This arrangement does not occur in flagella.

Exercise:

Problem: How do cilia and flagella differ?

Solution:

Cilia and flagella are alike in that they are made up of microtubules. Cilia are short, hair-like structures that exist in large numbers and usually cover the entire surface of the plasma membrane. Flagella, in contrast, are long, hair-like structures; when flagella are present, a cell has just one or two.

Glossary

cilium
> (plural = cilia) short, hair-like structure that extends from the plasma membrane in large numbers and is used to move an entire cell or move substances along the outer surface of the cell

cytoskeleton
> network of protein fibers that collectively maintain the shape of the cell, secure some organelles in specific positions, allow cytoplasm and vesicles to move within the cell, and enable unicellular organisms to move independently

flagellum
> (plural = flagella) long, hair-like structure that extends from the plasma membrane and is used to move the cell

intermediate filament
> cytoskeletal component, composed of several intertwined strands of fibrous protein, that bears tension, supports cell-cell junctions, and anchors cells to extracellular structures

microfilament
    narrowest element of the cytoskeleton system; it provides rigidity and shape to the
    cell and enables cellular movements

microtubule
    widest element of the cytoskeleton system; it helps the cell resist compression,
    provides a track along which vesicles move through the cell, pulls replicated
    chromosomes to opposite ends of a dividing cell, and is the structural element of
    centrioles, flagella, and cilia

Connections between Cells and Cellular Activities
By the end of this section, you will be able to:

- Describe the extracellular matrix
- List examples of the ways that plant cells and animal cells communicate with adjacent cells
- Summarize the roles of tight junctions, desmosomes, gap junctions, and plasmodesmata

You already know that a group of similar cells working together is called a tissue. As you might expect, if cells are to work together, they must communicate with each other, just as you need to communicate with others if you work on a group project. Let's take a look at how cells communicate with each other.

Extracellular Matrix of Animal Cells

Most animal cells release materials into the extracellular space. The primary components of these materials are proteins, and the most abundant protein is collagen. Collagen fibers are interwoven with carbohydrate-containing protein molecules called proteoglycans. Collectively, these materials are called the **extracellular matrix** ([link]). Not only does the extracellular matrix hold the cells together to form a tissue, but it also allows the cells within the tissue to communicate with each other. How can this happen?
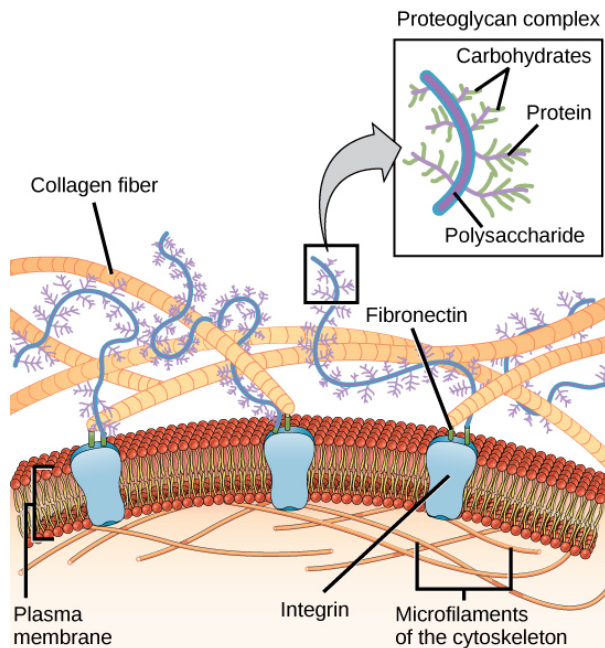
The extracellular matrix consists of a network of proteins and carbohydrates.

Cells have protein receptors on the extracellular surfaces of their plasma membranes. When a molecule within the matrix binds to the receptor, it changes the molecular structure of the receptor. The receptor, in turn, changes the conformation of the microfilaments positioned just inside the plasma membrane. These conformational changes induce chemical signals inside the cell that reach the nucleus and turn "on" or "off" the transcription of specific sections of DNA, which affects the production of associated proteins, thus changing the activities within the cell.

Blood clotting provides an example of the role of the extracellular matrix in cell communication. When the cells lining a blood vessel are damaged, they display a protein receptor called tissue factor. When tissue factor binds with another factor in the extracellular matrix, it causes platelets to adhere to the wall of the damaged blood vessel, stimulates the adjacent smooth muscle cells in the blood vessel to contract (thus constricting the blood vessel), and

initiates a series of steps that stimulate the platelets to produce clotting factors.

Intercellular Junctions

Cells can also communicate with each other via direct contact, referred to as intercellular junctions. There are some differences in the ways that plant and animal cells do this. Plasmodesmata are junctions between plant cells, whereas animal cell contacts include tight junctions, gap junctions, and desmosomes.

Plasmodesmata

In general, long stretches of the plasma membranes of neighboring plant cells cannot touch one another because they are separated by the cell wall that surrounds each cell ([link]**b**). How then, can a plant transfer water and other soil nutrients from its roots, through its stems, and to its leaves? Such transport uses the vascular tissues (xylem and phloem) primarily. There also exist structural modifications called **plasmodesmata** (singular = plasmodesma), numerous channels that pass between cell walls of adjacent plant cells, connect their cytoplasm, and enable materials to be transported from cell to cell, and thus throughout the plant ([link]).
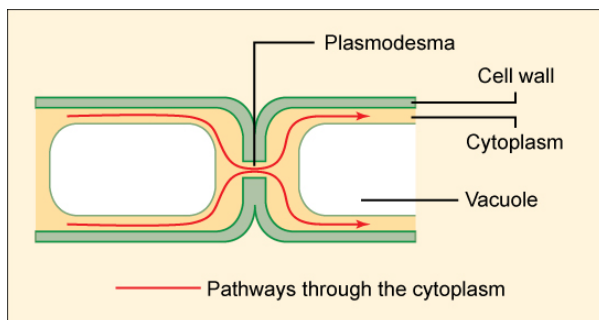
A plasmodesma is a channel between the cell walls of two adjacent plant cells.

Plasmodesmata allow materials to pass from the cytoplasm of one plant cell to the cytoplasm of an adjacent cell.

Tight Junctions

A **tight junction** is a watertight seal between two adjacent animal cells ([link]). The cells are held tightly against each other by proteins (predominantly two proteins called claudins and occludins).
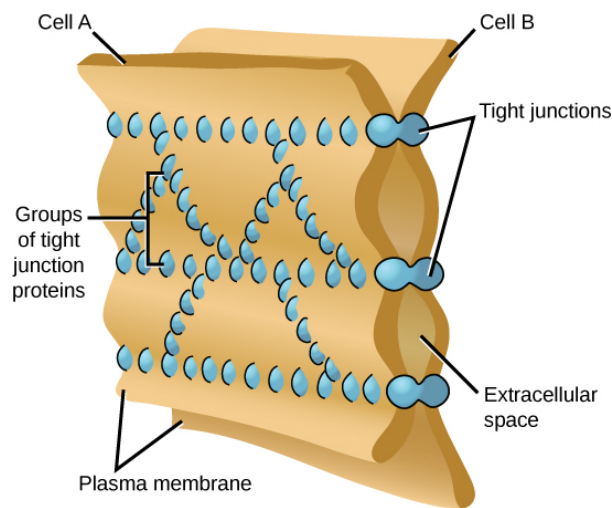
Tight junctions form watertight connections between adjacent animal cells. Proteins create tight junction adherence. (credit: modification of work by Mariana Ruiz Villareal)

This tight adherence prevents materials from leaking between the cells; tight junctions are typically found in epithelial tissues that line internal organs and cavities, and comprise most of the skin. For example, the tight junctions of the epithelial cells lining your urinary bladder prevent urine from leaking out into the extracellular space.
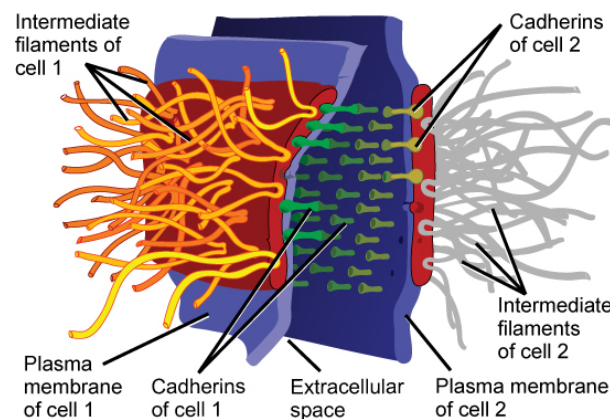
Desmosomes

Also found only in animal cells are **desmosomes**, which act like spot welds between adjacent epithelial cells ([link]). Short proteins called cadherins in the plasma membrane connect to intermediate filaments to create desmosomes. The cadherins join two adjacent cells together and maintain the cells in a sheet-like formation in organs and tissues that stretch, like the skin, heart, and muscles.

A desmosome forms a very strong spot weld between cells. It is created by the linkage of cadherins and intermediate filaments. (credit: modification of work by Mariana Ruiz Villareal)

Gap Junctions

Gap junctions in animal cells are like plasmodesmata in plant cells in that they are channels between adjacent cells that allow for the transport of ions, nutrients, and other substances that enable cells to communicate ([link]). Structurally, however, gap junctions and plasmodesmata differ.
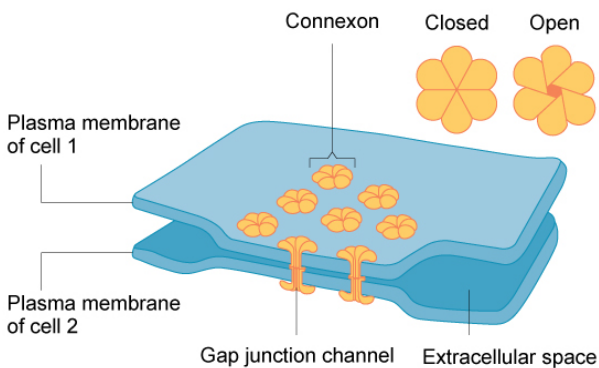
A gap junction is a protein-lined pore that allows water and small molecules to pass between adjacent animal cells. (credit: modification of work by Mariana Ruiz Villareal)

Gap junctions develop when a set of six proteins (called connexins) in the plasma membrane arrange themselves in an elongated donut-like configuration called a connexon. When the pores ("doughnut holes") of connexons in adjacent animal cells align, a channel between the two cells forms. Gap junctions are particularly important in cardiac muscle: The electrical signal for the muscle to contract is passed efficiently through gap junctions, allowing the heart muscle cells to contract in tandem.

Note:

Section Summary

Animal cells communicate via their extracellular matrices and are connected to each other via tight junctions, desmosomes, and gap junctions. Plant cells are connected and communicate with each other via plasmodesmata.

When protein receptors on the surface of the plasma membrane of an animal cell bind to a substance in the extracellular matrix, a chain of reactions begins that changes activities taking place within the cell. Plasmodesmata are channels between adjacent plant cells, while gap junctions are channels between adjacent animal cells. However, their structures are quite different. A tight junction is a watertight seal between two adjacent cells, while a desmosome acts like a spot weld.

Review Questions

Exercise:

   Problem: Which of the following are found only in plant cells?

   a. gap junctions
   b. desmosomes
   c. plasmodesmata

d. tight junctions

Solution:

C

Exercise:

Problem:

The key components of desmosomes are cadherins and _____.

a. actin
b. microfilaments
c. intermediate filaments
d. microtubules

Solution:

C

Free Response

Exercise:

Problem:

How does the structure of a plasmodesma differ from that of a gap junction?

Solution:

They differ because plant cell walls are rigid. Plasmodesmata, which a plant cell needs for transportation and communication, are able to allow movement of really large molecules. Gap junctions are necessary in animal cells for transportation and communication.

Exercise:

Problem: Explain how the extracellular matrix functions.

Solution:

The extracellular matrix functions in support and attachment for animal tissues. It also functions in the healing and growth of the tissue.

Glossary

desmosome
> linkages between adjacent epithelial cells that form when cadherins in the plasma membrane attach to intermediate filaments

extracellular matrix
> material (primarily collagen, glycoproteins, and proteoglycans) secreted from animal cells that provides mechanical protection and anchoring for the cells in the tissue

gap junction
> channel between two adjacent animal cells that allows ions, nutrients, and low molecular weight substances to pass between cells, enabling the cells to communicate

plasmodesma
> (plural = plasmodesmata) channel that passes between the cell walls of adjacent plant cells, connects their cytoplasm, and allows materials to be transported from cell to cell

tight junction
> firm seal between two adjacent animal cells created by protein adherence

Introduction class="introduction"

Despite its seeming hustle and bustle, Grand Central Station functions with a high level of organization: People and objects move from one location to another, they cross or are contained within certain boundaries, and they provide a constant flow as part of larger activity. Analogously, a plasma membrane's functions involve movement

within the cell and across boundaries in the process of intracellular and intercellular activities. (credit: modification of work by Randy Le'Moine)

The plasma membrane, which is also called the cell membrane, has many functions, but the most basic one is to define the borders of the cell and keep the cell functional. The plasma membrane is selectively permeable. This means that the membrane allows some materials to freely enter or leave the cell, while other materials cannot move freely, but require the use

of a specialized structure, and occasionally, even energy investment for crossing.

Components and Structure
By the end of this section, you will be able to:

- Understand the fluid mosaic model of cell membranes
- Describe the functions of phospholipids, proteins, and carbohydrates in membranes
- Discuss membrane fluidity

A cell's plasma membrane defines the cell, outlines its borders, and determines the nature of its interaction with its environment (see [link] for a summary). Cells exclude some substances, take in others, and excrete still others, all in controlled quantities. The plasma membrane must be very flexible to allow certain cells, such as red blood cells and white blood cells, to change shape as they pass through narrow capillaries. These are the more obvious functions of a plasma membrane. In addition, the surface of the plasma membrane carries markers that allow cells to recognize one another, which is vital for tissue and organ formation during early development, and which later plays a role in the "self" versus "non-self" distinction of the immune response.

Among the most sophisticated functions of the plasma membrane is the ability to transmit signals by means of complex, integral proteins known as receptors. These proteins act both as receivers of extracellular inputs and as activators of intracellular processes. These membrane receptors provide extracellular attachment sites for effectors like hormones and growth factors, and they activate intracellular response cascades when their effectors are bound. Occasionally, receptors are hijacked by viruses (HIV, human immunodeficiency virus, is one example) that use them to gain entry into cells, and at times, the genes encoding receptors become mutated, causing the process of signal transduction to malfunction with disastrous consequences.

Fluid Mosaic Model

The existence of the plasma membrane was identified in the 1890s, and its chemical components were identified in 1915. The principal components identified at that time were lipids and proteins. The first widely accepted

model of the plasma membrane's structure was proposed in 1935 by Hugh Davson and James Danielli; it was based on the "railroad track" appearance of the plasma membrane in early electron micrographs. They theorized that the structure of the plasma membrane resembles a sandwich, with protein being analogous to the bread, and lipids being analogous to the filling. In the 1950s, advances in microscopy, notably transmission electron microscopy (TEM), allowed researchers to see that the core of the plasma membrane consisted of a double, rather than a single, layer. A new model that better explains both the microscopic observations and the function of that plasma membrane was proposed by S.J. Singer and Garth L. Nicolson in 1972.

The explanation proposed by Singer and Nicolson is called the **fluid mosaic model**. The model has evolved somewhat over time, but it still best accounts for the structure and functions of the plasma membrane as we now understand them. The fluid mosaic model describes the structure of the plasma membrane as a mosaic of components—including phospholipids, cholesterol, proteins, and carbohydrates—that gives the membrane a fluid character. Plasma membranes range from 5 to 10 nm in thickness. For comparison, human red blood cells, visible via light microscopy, are approximately 8 µm wide, or approximately 1,000 times wider than a plasma membrane. The membrane does look a bit like a sandwich ([link]).

Glycoprotein: protein with carbohydrate attached

Glycolipid: lipid with carbohydrate attached

Peripheral membrane protein

Integral membrane protein

Cytoskeletal filaments

Cholesterol

Protein channel

Phospholipid bilayer
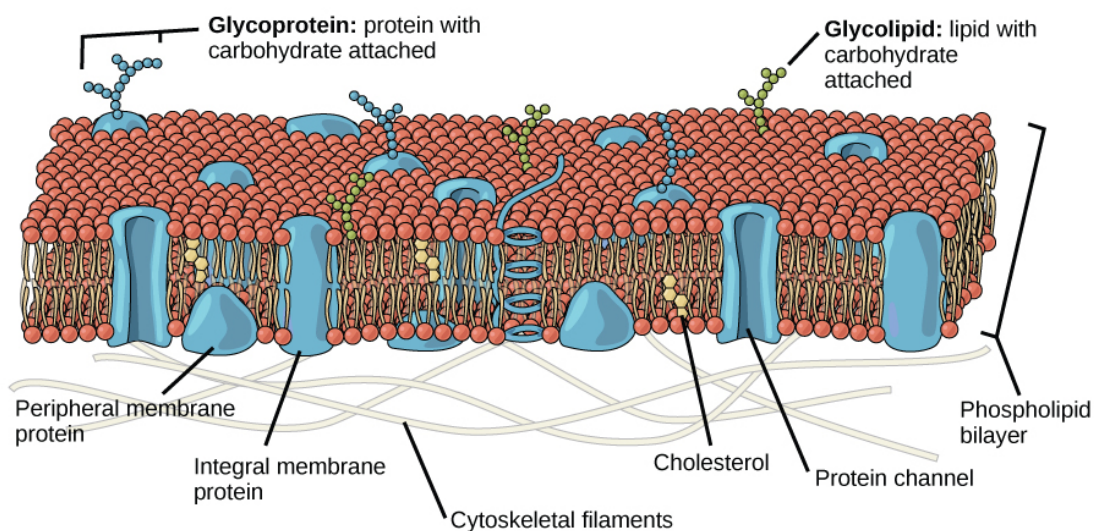
The fluid mosaic model of the plasma membrane describes the plasma membrane as a fluid combination of phospholipids, cholesterol, and proteins. Carbohydrates attached to lipids (glycolipids) and to proteins (glycoproteins) extend from the outward-facing surface of the membrane.
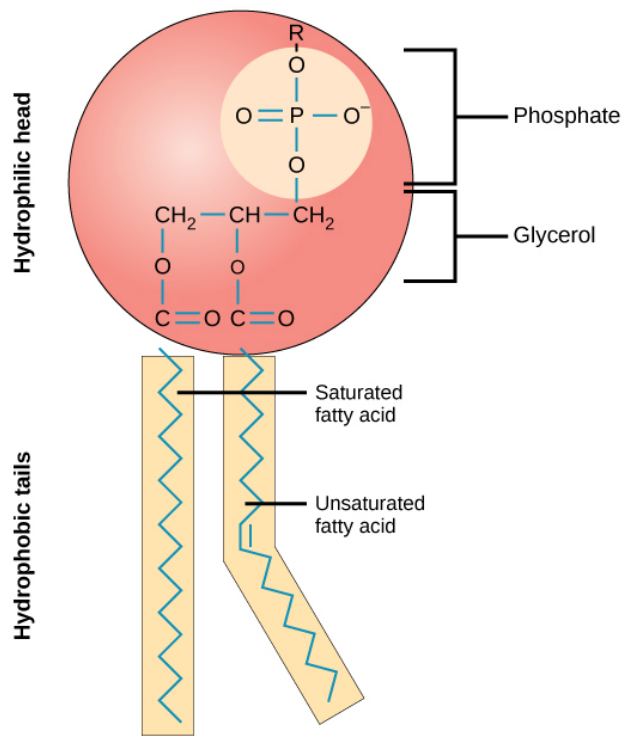
The principal components of a plasma membrane are lipids (phospholipids and cholesterol), proteins, and carbohydrates attached to some of the lipids and some of the proteins. A phospholipid is a molecule consisting of glycerol, two fatty acids, and a phosphate-linked head group. Cholesterol, another lipid composed of four fused carbon rings, is found alongside the phospholipids in the core of the membrane. The proportions of proteins, lipids, and carbohydrates in the plasma membrane vary with cell type, but for a typical human cell, protein accounts for about 50 percent of the composition by mass, lipids (of all types) account for about 40 percent of the composition by mass, with the remaining 10 percent of the composition by mass being carbohydrates. However, the concentration of proteins and lipids varies with different cell membranes. For example, myelin, an outgrowth of the membrane of specialized cells that insulates the axons of the peripheral nerves, contains only 18 percent protein and 76 percent lipid. The mitochondrial inner membrane contains 76 percent protein and only 24 percent lipid. The plasma membrane of human red blood cells is 30 percent lipid. Carbohydrates are present only on the exterior surface of the plasma membrane and are attached to proteins, forming **glycoproteins**, or attached to lipids, forming **glycolipids**.

Phospholipids

The main fabric of the membrane is composed of amphiphilic, phospholipid molecules. The **hydrophilic** or "water-loving" areas of these molecules (which look like a collection of balls in an artist's rendition of the model) ([link]) are in contact with the aqueous fluid both inside and outside the cell. **Hydrophobic**, or water-hating molecules, tend to be non-polar. They interact with other non-polar molecules in chemical reactions, but generally

do not interact with polar molecules. When placed in water, hydrophobic molecules tend to form a ball or cluster. The hydrophilic regions of the phospholipids tend to form hydrogen bonds with water and other polar molecules on both the exterior and interior of the cell. Thus, the membrane surfaces that face the interior and exterior of the cell are hydrophilic. In contrast, the interior of the cell membrane is hydrophobic and will not interact with water. Therefore, phospholipids form an excellent two-layer cell membrane that separates fluid within the cell from the fluid outside of the cell.

A phospholipid molecule ([link]) consists of a three-carbon glycerol backbone with two fatty acid molecules attached to carbons 1 and 2, and a phosphate-containing group attached to the third carbon. This arrangement gives the overall molecule an area described as its head (the phosphate-containing group), which has a polar character or negative charge, and an area called the tail (the fatty acids), which has no charge. The head can form hydrogen bonds, but the tail cannot. A molecule with this arrangement of a positively or negatively charged area and an uncharged, or non-polar, area is referred to as **amphiphilic** or "dual-loving."

The figure shows a phospholipid molecule with labels:

- **Hydrophilic head** (left side, rotated label)
- **Hydrophobic tails** (left side, rotated label)

Within the head group:
- R
- O
- O=P—O⁻

Structure: $O = P - O^-$ with $R-O$ above and O below.

- Phosphate
- $CH_2 - CH - CH_2$ with attached O groups
- Glycerol
- $C = O \quad C = O$
- Saturated fatty acid
- Unsaturated fatty acid

This phospholipid molecule is composed of a hydrophilic head and two hydrophobic tails. The hydrophilic head group consists of a phosphate-containing group attached to a glycerol molecule. The hydrophobic tails, each containing either a saturated or an unsaturated fatty acid, are long hydrocarbon chains.

This characteristic is vital to the structure of a plasma membrane because, in water, phospholipids tend to become arranged with their hydrophobic tails facing each other and their hydrophilic heads facing out. In this way, they form a lipid bilayer—a barrier composed of a double layer of phospholipids that separates the water and other materials on one side of the barrier from the water and other materials on the other side. In fact, phospholipids heated in an aqueous solution tend to spontaneously form

small spheres or droplets (called micelles or liposomes), with their hydrophilic heads forming the exterior and their hydrophobic tails on the inside ([link]).

Lipid-bilayer sphere

Single-layer lipid sphere

Lipid-bilayer sheet
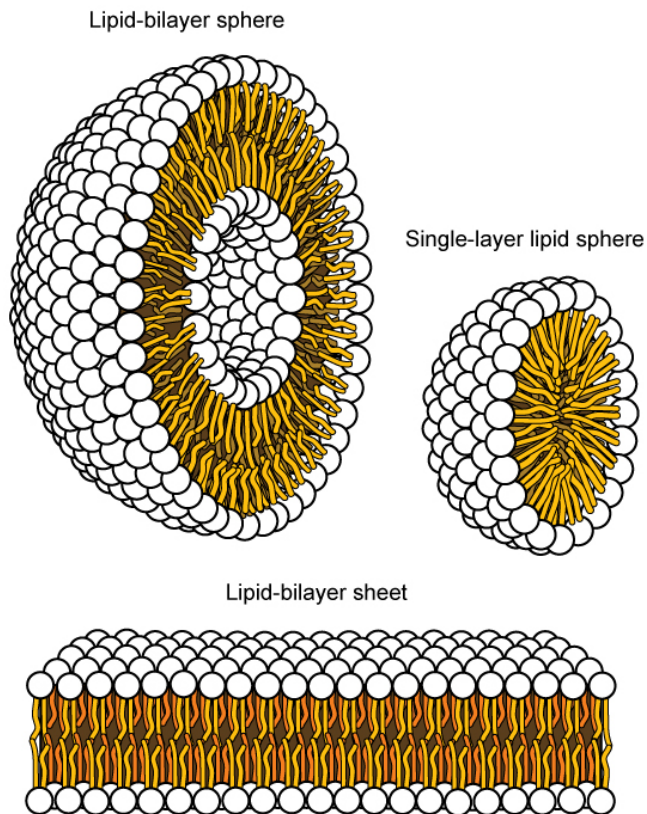
In an aqueous solution, phospholipids tend to arrange themselves with their polar heads facing outward and their hydrophobic tails facing inward. (credit: modification of work by Mariana Ruiz Villareal)

Proteins

Proteins make up the second major component of plasma membranes. **Integral proteins** (some specialized types are called integrins) are, as their name suggests, integrated completely into the membrane structure, and their hydrophobic membrane-spanning regions interact with the hydrophobic region of the the phospholipid bilayer ([link]). Single-pass integral membrane proteins usually have a hydrophobic transmembrane segment that consists of 20–25 amino acids. Some span only part of the membrane—associating with a single layer—while others stretch from one side of the membrane to the other, and are exposed on either side. Some complex proteins are composed of up to 12 segments of a single protein, which are extensively folded and embedded in the membrane ([link]). This type of protein has a hydrophilic region or regions, and one or several mildly hydrophobic regions. This arrangement of regions of the protein tends to orient the protein alongside the phospholipids, with the hydrophobic region of the protein adjacent to the tails of the phospholipids and the hydrophilic region or regions of the protein protruding from the membrane and in contact with the cytosol or extracellular fluid.
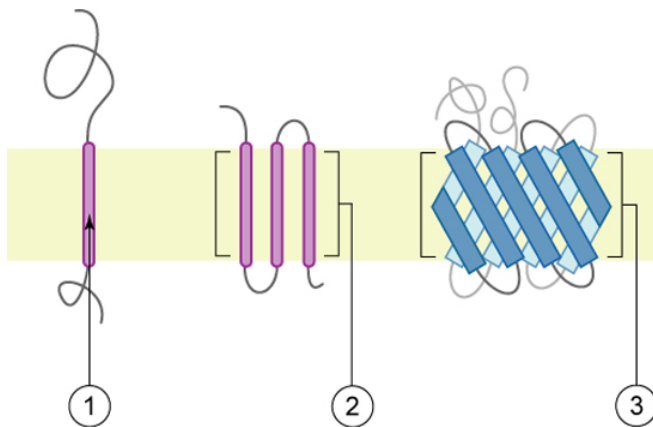
Integral membranes proteins may have one or more alpha-helices that span the membrane (examples 1 and 2), or they may have beta-sheets that span the membrane (example 3). (credit: "Foobar"/Wikimedia Commons)

Peripheral proteins are found on the exterior and interior surfaces of membranes, attached either to integral proteins or to phospholipids. Peripheral proteins, along with integral proteins, may serve as enzymes, as structural attachments for the fibers of the cytoskeleton, or as part of the cell's recognition sites. These are sometimes referred to as "cell-specific" proteins. The body recognizes its own proteins and attacks foreign proteins associated with invasive pathogens.

Carbohydrates

Carbohydrates are the third major component of plasma membranes. They are always found on the exterior surface of cells and are bound either to proteins (forming glycoproteins) or to lipids (forming glycolipids) ([link]). These carbohydrate chains may consist of 2–60 monosaccharide units and can be either straight or branched. Along with peripheral proteins, carbohydrates form specialized sites on the cell surface that allow cells to recognize each other. These sites have unique patterns that allow the cell to be recognized, much the way that the facial features unique to each person allow him or her to be recognized. This recognition function is very important to cells, as it allows the immune system to differentiate between body cells (called "self") and foreign cells or tissues (called "non-self"). Similar types of glycoproteins and glycolipids are found on the surfaces of viruses and may change frequently, preventing immune cells from recognizing and attacking them.

These carbohydrates on the exterior surface of the cell—the carbohydrate components of both glycoproteins and glycolipids—are collectively referred to as the glycocalyx (meaning "sugar coating"). The glycocalyx is highly hydrophilic and attracts large amounts of water to the surface of the cell. This aids in the interaction of the cell with its watery environment and in the cell's ability to obtain substances dissolved in the water. As discussed above, the glycocalyx is also important for cell identification, self/non-self

determination, and embryonic development, and is used in cell-cell attachments to form tissues.

Note:
Evolution Connection
How Viruses Infect Specific Organs
Glycoprotein and glycolipid patterns on the surfaces of cells give many viruses an opportunity for infection. HIV and hepatitis viruses infect only specific organs or cells in the human body. HIV is able to penetrate the plasma membranes of a subtype of lymphocytes called T-helper cells, as well as some monocytes and central nervous system cells. The hepatitis virus attacks liver cells.
These viruses are able to invade these cells, because the cells have binding sites on their surfaces that are specific to and compatible with certain viruses ([link]). Other recognition sites on the virus's surface interact with the human immune system, prompting the body to produce antibodies. Antibodies are made in response to the antigens or proteins associated with invasive pathogens, or in response to foreign cells, such as might occur with an organ transplant. These same sites serve as places for antibodies to attach and either destroy or inhibit the activity of the virus. Unfortunately, these recognition sites on HIV change at a rapid rate because of mutations, making the production of an effective vaccine against the virus very difficult, as the virus evolves and adapts. A person infected with HIV will quickly develop different populations, or variants, of the virus that are distinguished by differences in these recognition sites. This rapid change of surface markers decreases the effectiveness of the person's immune system in attacking the virus, because the antibodies will not recognize the new variations of the surface patterns. In the case of HIV, the problem is compounded by the fact that the virus specifically infects and destroys cells involved in the immune response, further incapacitating the host.
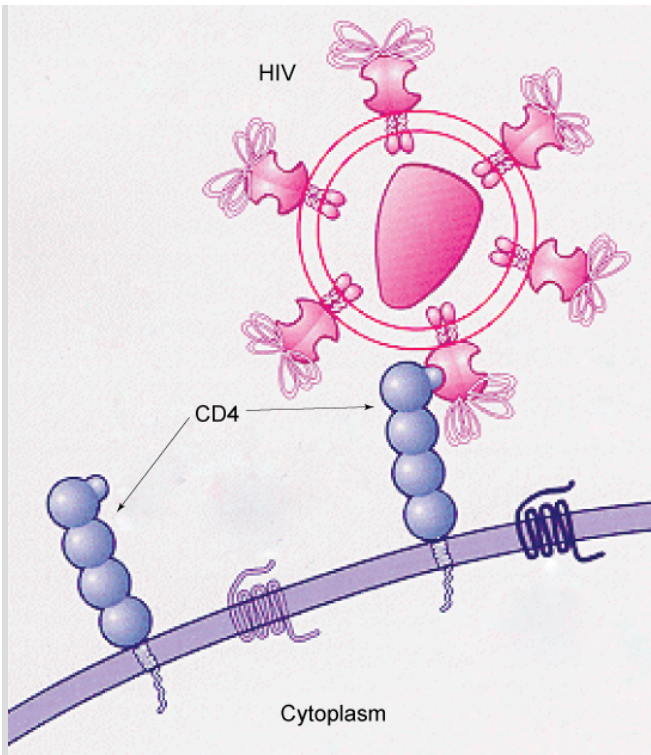
HIV binds to the CD4 receptor, a glycoprotein on the surfaces of T cells. (credit: modification of work by NIH, NIAID)

Membrane Fluidity

The mosaic characteristic of the membrane, described in the fluid mosaic model, helps to illustrate its nature. The integral proteins and lipids exist in the membrane as separate but loosely attached molecules. These resemble the separate, multicolored tiles of a mosaic picture, and they float, moving somewhat with respect to one another. The membrane is not like a balloon, however, that can expand and contract; rather, it is fairly rigid and can burst if penetrated or if a cell takes in too much water. However, because of its mosaic nature, a very fine needle can easily penetrate a plasma membrane

without causing it to burst, and the membrane will flow and self-seal when the needle is extracted.

The mosaic characteristics of the membrane explain some but not all of its fluidity. There are two other factors that help maintain this fluid characteristic. One factor is the nature of the phospholipids themselves. In their saturated form, the fatty acids in phospholipid tails are saturated with bound hydrogen atoms. There are no double bonds between adjacent carbon atoms. This results in tails that are relatively straight. In contrast, unsaturated fatty acids do not contain a maximal number of hydrogen atoms, but they do contain some double bonds between adjacent carbon atoms; a double bond results in a bend in the string of carbons of approximately 30 degrees ([link]).

Thus, if saturated fatty acids, with their straight tails, are compressed by decreasing temperatures, they press in on each other, making a dense and fairly rigid membrane. If unsaturated fatty acids are compressed, the "kinks" in their tails elbow adjacent phospholipid molecules away, maintaining some space between the phospholipid molecules. This "elbow room" helps to maintain fluidity in the membrane at temperatures at which membranes with saturated fatty acid tails in their phospholipids would "freeze" or solidify. The relative fluidity of the membrane is particularly important in a cold environment. A cold environment tends to compress membranes composed largely of saturated fatty acids, making them less fluid and more susceptible to rupturing. Many organisms (fish are one example) are capable of adapting to cold environments by changing the proportion of unsaturated fatty acids in their membranes in response to the lowering of the temperature.

Note:
Link to Learning

Animals have an additional membrane constituent that assists in maintaining fluidity. Cholesterol, which lies alongside the phospholipids in the membrane, tends to dampen the effects of temperature on the membrane. Thus, this lipid functions as a buffer, preventing lower temperatures from inhibiting fluidity and preventing increased temperatures from increasing fluidity too much. Thus, cholesterol extends, in both directions, the range of temperature in which the membrane is appropriately fluid and consequently functional. Cholesterol also serves other functions, such as organizing clusters of transmembrane proteins into lipid rafts.

The Components and Functions of the Plasma Membrane	
Component	**Location**
Phospholipid	Main fabric of the membrane
Cholesterol	Attached between phospholipids and between the two phospholipid layers

The Components and Functions of the Plasma Membrane	
Component	**Location**
Integral proteins (for example, integrins)	Embedded within the phospholipid layer(s). May or may not penetrate through both layers
Peripheral proteins	On the inner or outer surface of the phospholipid bilayer; not embedded within the phospholipids
Carbohydrates (components of glycoproteins and glycolipids)	Generally attached to proteins on the outside membrane layer

Note:
Career Connection
Immunologist
The variations in peripheral proteins and carbohydrates that affect a cell's recognition sites are of prime interest in immunology. These changes are taken into consideration in vaccine development. Many infectious diseases, such as smallpox, polio, diphtheria, and tetanus, were conquered by the use of vaccines.
Immunologists are the physicians and scientists who research and develop vaccines, as well as treat and study allergies or other immune problems. Some immunologists study and treat autoimmune problems (diseases in which a person's immune system attacks his or her own cells or tissues, such as lupus) and immunodeficiencies, whether acquired (such as acquired immunodeficiency syndrome, or AIDS) or hereditary (such as severe combined immunodeficiency, or SCID). Immunologists are called in to help treat organ transplantation patients, who must have their immune systems suppressed so that their bodies will not reject a transplanted organ.

Some immunologists work to understand natural immunity and the effects of a person's environment on it. Others work on questions about how the immune system affects diseases such as cancer. In the past, the importance of having a healthy immune system in preventing cancer was not at all understood.

To work as an immunologist, a PhD or MD is required. In addition, immunologists undertake at least 2–3 years of training in an accredited program and must pass an examination given by the American Board of Allergy and Immunology. Immunologists must possess knowledge of the functions of the human body as they relate to issues beyond immunization, and knowledge of pharmacology and medical technology, such as medications, therapies, test materials, and surgical procedures.

Section Summary

The modern understanding of the plasma membrane is referred to as the fluid mosaic model. The plasma membrane is composed of a bilayer of phospholipids, with their hydrophobic, fatty acid tails in contact with each other. The landscape of the membrane is studded with proteins, some of which span the membrane. Some of these proteins serve to transport materials into or out of the cell. Carbohydrates are attached to some of the proteins and lipids on the outward-facing surface of the membrane, forming complexes that function to identify the cell to other cells. The fluid nature of the membrane is due to temperature, the configuration of the fatty acid tails (some kinked by double bonds), the presence of cholesterol embedded in the membrane, and the mosaic nature of the proteins and protein-carbohydrate combinations, which are not firmly fixed in place. Plasma membranes enclose and define the borders of cells, but rather than being a static bag, they are dynamic and constantly in flux.

Review Questions

Exercise:

Problem:

Which plasma membrane component can be either found on its surface or embedded in the membrane structure?

   a. protein
   b. cholesterol
   c. carbohydrate
   d. phospholipid

Solution:

A

Exercise:

Problem:

Which characteristic of a phospholipid contributes to the fluidity of the membrane?

   a. its head
   b. cholesterol
   c. a saturated fatty acid tail
   d. double bonds in the fatty acid tail

Solution:

D

Exercise:

Problem:

What is the primary function of carbohydrates attached to the exterior of cell membranes?

   a. identification of the cell

b. flexibility of the membrane

c. strengthening the membrane

d. channels through membrane

Solution:

A

Free Response

Exercise:

Problem:

Why is it advantageous for the cell membrane to be fluid in nature?

Solution:

The fluid characteristic of the cell membrane allows greater flexibility to the cell than it would if the membrane were rigid. It also allows the motion of membrane components, required for some types of membrane transport.

Exercise:

Problem:

Why do phospholipids tend to spontaneously orient themselves into something resembling a membrane?

Solution:

The hydrophobic, nonpolar regions must align with each other in order for the structure to have minimal potential energy and, consequently, higher stability. The fatty acid tails of the phospholipids cannot mix with water, but the phosphate "head" of the molecule can. Thus, the head orients to water, and the tail to other lipids.

Glossary

amphiphilic
> molecule possessing a polar or charged area and a nonpolar or uncharged area capable of interacting with both hydrophilic and hydrophobic environments

fluid mosaic model
> describes the structure of the plasma membrane as a mosaic of components including phospholipids, cholesterol, proteins, glycoproteins, and glycolipids (sugar chains attached to proteins or lipids, respectively), resulting in a fluid character (fluidity)

glycolipid
> combination of carbohydrates and lipids

glycoprotein
> combination of carbohydrates and proteins

hydrophilic
> molecule with the ability to bond with water; "water-loving"

hydrophobic
> molecule that does not have the ability to bond with water; "water-hating"

integral protein
> protein integrated into the membrane structure that interacts extensively with the hydrocarbon chains of membrane lipids and often spans the membrane; these proteins can be removed only by the disruption of the membrane by detergents

peripheral protein
> protein found at the surface of a plasma membrane either on its exterior or interior side; these proteins can be removed (washed off of the membrane) by a high-salt wash

Passive Transport
By the end of this section, you will be able to:

- Explain why and how passive transport occurs
- Understand the processes of osmosis and diffusion
- Define tonicity and describe its relevance to passive transport

Plasma membranes must allow certain substances to enter and leave a cell, and prevent some harmful materials from entering and some essential materials from leaving. In other words, plasma membranes are **selectively permeable**—they allow some substances to pass through, but not others. If they were to lose this selectivity, the cell would no longer be able to sustain itself, and it would be destroyed. Some cells require larger amounts of specific substances than do other cells; they must have a way of obtaining these materials from extracellular fluids. This may happen passively, as certain materials move back and forth, or the cell may have special mechanisms that facilitate transport. Some materials are so important to a cell that it spends some of its energy, hydrolyzing adenosine triphosphate (ATP), to obtain these materials. Red blood cells use some of their energy doing just that. All cells spend the majority of their energy to maintain an imbalance of sodium and potassium ions between the interior and exterior of the cell.

The most direct forms of membrane transport are passive. **Passive transport** is a naturally occurring phenomenon and does not require the cell to exert any of its energy to accomplish the movement. In passive transport, substances move from an area of higher concentration to an area of lower concentration. A physical space in which there is a range of concentrations of a single substance is said to have a **concentration gradient**.

Selective Permeability

Plasma membranes are asymmetric: the interior of the membrane is not identical to the exterior of the membrane. In fact, there is a considerable difference between the array of phospholipids and proteins between the two leaflets that form a membrane. On the interior of the membrane, some proteins serve to anchor the membrane to fibers of the cytoskeleton. There

are peripheral proteins on the exterior of the membrane that bind elements of the extracellular matrix. Carbohydrates, attached to lipids or proteins, are also found on the exterior surface of the plasma membrane. These carbohydrate complexes help the cell bind substances that the cell needs in the extracellular fluid. This adds considerably to the selective nature of plasma membranes ([link]).
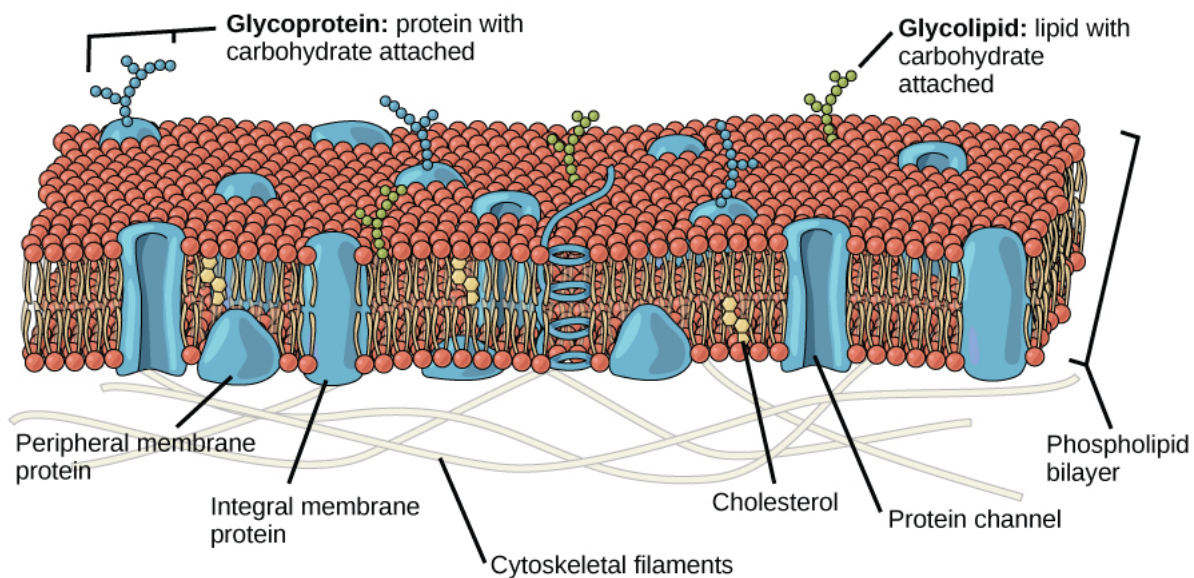

The exterior surface of the plasma membrane is not identical to the interior surface of the same membrane.

Recall that plasma membranes are amphiphilic: They have hydrophilic and hydrophobic regions. This characteristic helps the movement of some materials through the membrane and hinders the movement of others. Lipid-soluble material with a low molecular weight can easily slip through the hydrophobic lipid core of the membrane. Substances such as the fat-soluble vitamins A, D, E, and K readily pass through the plasma membranes in the digestive tract and other tissues. Fat-soluble drugs and hormones also gain easy entry into cells and are readily transported into the body's tissues and organs. Molecules of oxygen and carbon dioxide have no charge and so pass through membranes by simple diffusion.

Polar substances present problems for the membrane. While some polar molecules connect easily with the outside of a cell, they cannot readily pass through the lipid core of the plasma membrane. Additionally, while small ions could easily slip through the spaces in the mosaic of the membrane, their charge prevents them from doing so. Ions such as sodium, potassium, calcium, and chloride must have special means of penetrating plasma membranes. Simple sugars and amino acids also need help with transport across plasma membranes, achieved by various transmembrane proteins (channels).

Diffusion

Diffusion is a passive process of transport. A single substance tends to move from an area of high concentration to an area of low concentration until the concentration is equal across a space. You are familiar with diffusion of substances through the air. For example, think about someone opening a bottle of ammonia in a room filled with people. The ammonia gas is at its highest concentration in the bottle; its lowest concentration is at the edges of the room. The ammonia vapor will diffuse, or spread away, from the bottle, and gradually, more and more people will smell the ammonia as it spreads. Materials move within the cell's cytosol by diffusion, and certain materials move through the plasma membrane by diffusion ([link]). Diffusion expends no energy. On the contrary, concentration gradients are a form of potential energy, dissipated as the gradient is eliminated.
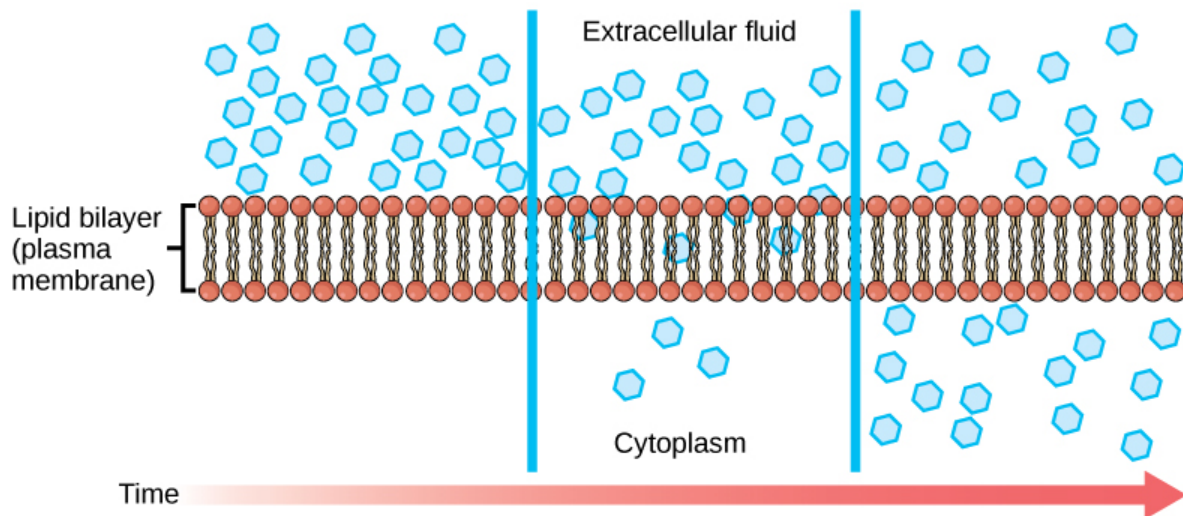
Diffusion through a permeable membrane moves a substance from an area of high concentration (extracellular fluid, in this case) down its concentration gradient (into the cytoplasm). (credit: modification of work by Mariana Ruiz Villareal)

Each separate substance in a medium, such as the extracellular fluid, has its own concentration gradient, independent of the concentration gradients of other materials. In addition, each substance will diffuse according to that gradient. Within a system, there will be different rates of diffusion of the different substances in the medium.

Factors That Affect Diffusion

Molecules move constantly in a random manner, at a rate that depends on their mass, their environment, and the amount of thermal energy they possess, which in turn is a function of temperature. This movement accounts for the diffusion of molecules through whatever medium in which they are localized. A substance will tend to move into any space available to it until it is evenly distributed throughout it. After a substance has diffused completely through a space, removing its concentration gradient, molecules will still move around in the space, but there will be no *net*

movement of the number of molecules from one area to another. This lack of a concentration gradient in which there is no net movement of a substance is known as dynamic equilibrium. While diffusion will go forward in the presence of a concentration gradient of a substance, several factors affect the rate of diffusion.

- Extent of the concentration gradient: The greater the difference in concentration, the more rapid the diffusion. The closer the distribution of the material gets to equilibrium, the slower the rate of diffusion becomes.
- Mass of the molecules diffusing: Heavier molecules move more slowly; therefore, they diffuse more slowly. The reverse is true for lighter molecules.
- Temperature: Higher temperatures increase the energy and therefore the movement of the molecules, increasing the rate of diffusion. Lower temperatures decrease the energy of the molecules, thus decreasing the rate of diffusion.
- Solvent density: As the density of a solvent increases, the rate of diffusion decreases. The molecules slow down because they have a more difficult time getting through the denser medium. If the medium is less dense, diffusion increases. Because cells primarily use diffusion to move materials within the cytoplasm, any increase in the cytoplasm's density will inhibit the movement of the materials. An example of this is a person experiencing dehydration. As the body's cells lose water, the rate of diffusion decreases in the cytoplasm, and the cells' functions deteriorate. Neurons tend to be very sensitive to this effect. Dehydration frequently leads to unconsciousness and possibly coma because of the decrease in diffusion rate within the cells.
- Solubility: As discussed earlier, nonpolar or lipid-soluble materials pass through plasma membranes more easily than polar materials, allowing a faster rate of diffusion.
- Surface area and thickness of the plasma membrane: Increased surface area increases the rate of diffusion, whereas a thicker membrane reduces it.
- Distance travelled: The greater the distance that a substance must travel, the slower the rate of diffusion. This places an upper limitation

on cell size. A large, spherical cell will die because nutrients or waste cannot reach or leave the center of the cell, respectively. Therefore, cells must either be small in size, as in the case of many prokaryotes, or be flattened, as with many single-celled eukaryotes.

A variation of diffusion is the process of filtration. In filtration, material moves according to its concentration gradient through a membrane; sometimes the rate of diffusion is enhanced by pressure, causing the substances to filter more rapidly. This occurs in the kidney, where blood pressure forces large amounts of water and accompanying dissolved substances, or **solutes**, out of the blood and into the renal tubules. The rate of diffusion in this instance is almost totally dependent on pressure. One of the effects of high blood pressure is the appearance of protein in the urine, which is "squeezed through" by the abnormally high pressure.
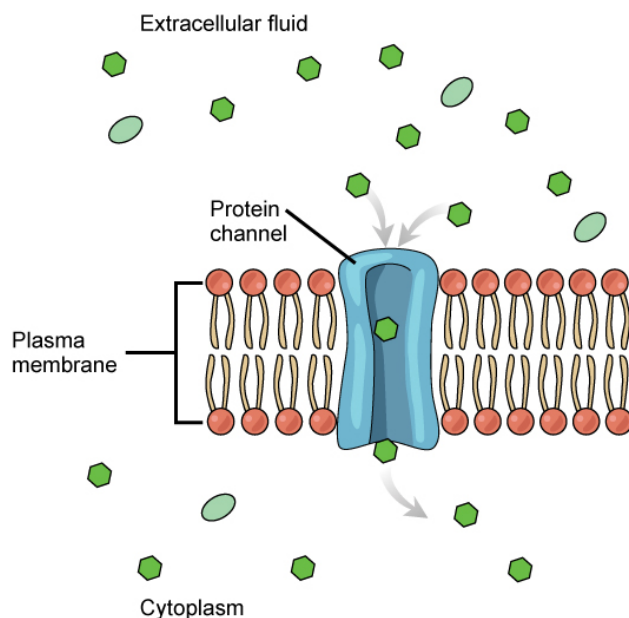
Facilitated transport

In **facilitated transport**, also called facilitated diffusion, materials diffuse across the plasma membrane with the help of membrane proteins. A concentration gradient exists that would allow these materials to diffuse into the cell without expending cellular energy. However, these materials are ions are polar molecules that are repelled by the hydrophobic parts of the cell membrane. Facilitated transport proteins shield these materials from the repulsive force of the membrane, allowing them to diffuse into the cell.

The material being transported is first attached to protein or glycoprotein receptors on the exterior surface of the plasma membrane. This allows the material that is needed by the cell to be removed from the extracellular fluid. The substances are then passed to specific integral proteins that facilitate their passage. Some of these integral proteins are collections of beta pleated sheets that form a pore or channel through the phospholipid bilayer. Others are carrier proteins which bind with the substance and aid its diffusion through the membrane.

Channels

The integral proteins involved in facilitated transport are collectively referred to as **transport proteins**, and they function as either channels for the material or carriers. In both cases, they are transmembrane proteins. Channels are specific for the substance that is being transported. **Channel proteins** have hydrophilic domains exposed to the intracellular and extracellular fluids; they additionally have a hydrophilic channel through their core that provides a hydrated opening through the membrane layers ([link]). Passage through the channel allows polar compounds to avoid the nonpolar central layer of the plasma membrane that would otherwise slow or prevent their entry into the cell. **Aquaporins** are channel proteins that allow water to pass through the membrane at a very high rate.
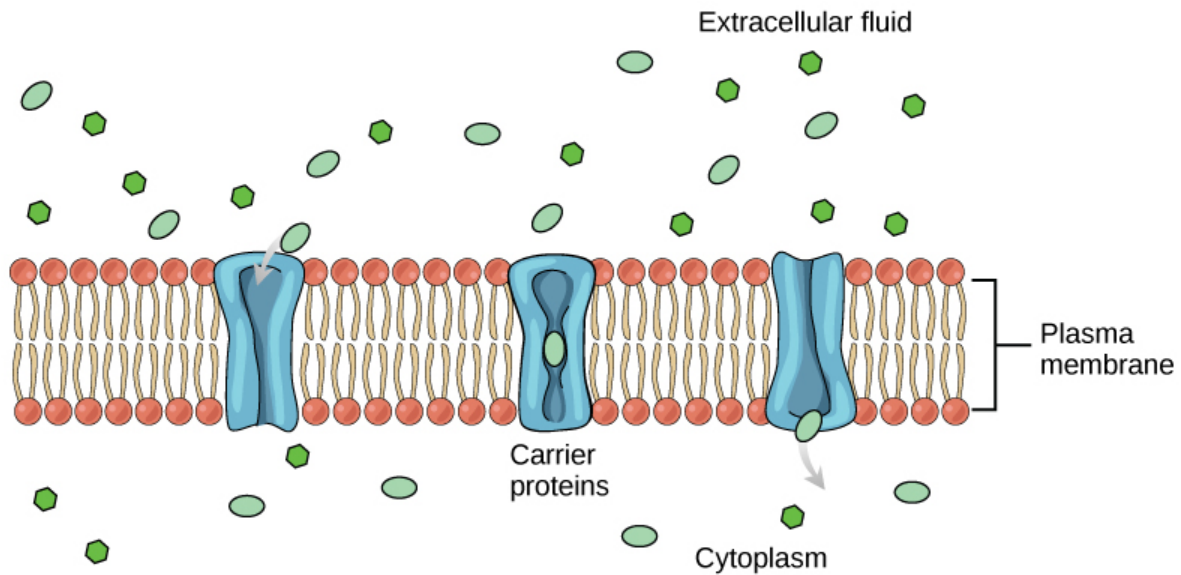

Facilitated transport moves substances down their concentration gradients. They may cross the plasma membrane with the aid of channel proteins. (credit: modification of work by Mariana Ruiz Villareal)

Channel proteins are either open at all times or they are "gated," which controls the opening of the channel. The attachment of a particular ion to the channel protein may control the opening, or other mechanisms or substances may be involved. In some tissues, sodium and chloride ions pass freely through open channels, whereas in other tissues a gate must be opened to allow passage. An example of this occurs in the kidney, where both forms of channels are found in different parts of the renal tubules. Cells involved in the transmission of electrical impulses, such as nerve and muscle cells, have gated channels for sodium, potassium, and calcium in their membranes. Opening and closing of these channels changes the relative concentrations on opposing sides of the membrane of these ions, resulting in the facilitation of electrical transmission along membranes (in the case of nerve cells) or in muscle contraction (in the case of muscle cells).

Carrier Proteins

Another type of protein embedded in the plasma membrane is a **carrier protein**. This aptly named protein binds a substance and, in doing so, triggers a change of its own shape, moving the bound molecule from the outside of the cell to its interior ([link]); depending on the gradient, the material may move in the opposite direction. Carrier proteins are typically specific for a single substance. This selectivity adds to the overall selectivity of the plasma membrane. The exact mechanism for the change of shape is poorly understood. Proteins can change shape when their hydrogen bonds are affected, but this may not fully explain this mechanism. Each carrier protein is specific to one substance, and there are a finite number of these proteins in any membrane. This can cause problems in transporting enough of the material for the cell to function properly. When all of the proteins are bound to their ligands, they are saturated and the rate of transport is at its maximum. Increasing the concentration gradient at this point will not result in an increased rate of transport.

Some substances are able to move down their concentration gradient across the plasma membrane with the aid of carrier proteins. Carrier proteins change shape as they move molecules across the membrane. (credit: modification of work by Mariana Ruiz Villareal)

An example of this process occurs in the kidney. Glucose, water, salts, ions, and amino acids needed by the body are filtered in one part of the kidney. This filtrate, which includes glucose, is then reabsorbed in another part of the kidney. Because there are only a finite number of carrier proteins for glucose, if more glucose is present than the proteins can handle, the excess is not transported and it is excreted from the body in the urine. In a diabetic individual, this is described as "spilling glucose into the urine." A different group of carrier proteins called glucose transport proteins, or GLUTs, are involved in transporting glucose and other hexose sugars through plasma membranes within the body.

Channel and carrier proteins transport material at different rates. Channel proteins transport much more quickly than do carrier proteins. Channel proteins facilitate diffusion at a rate of tens of millions of molecules per second, whereas carrier proteins work at a rate of a thousand to a million molecules per second.

Osmosis

Osmosis is the movement of water through a semipermeable membrane according to the concentration gradient of water across the membrane, which is inversely proportional to the concentration of solutes. While diffusion transports material across membranes and within cells, osmosis transports *only water* across a membrane and the membrane limits the diffusion of solutes in the water. Not surprisingly, the aquaporins that facilitate water movement play a large role in osmosis, most prominently in red blood cells and the membranes of kidney tubules.

Mechanism

Osmosis is a special case of diffusion. Water, like other substances, moves from an area of high concentration to one of low concentration. An obvious question is what makes water move at all? Imagine a beaker with a semipermeable membrane separating the two sides or halves ([link]). On both sides of the membrane the water level is the same, but there are different concentrations of a dissolved substance, or **solute**, that cannot cross the membrane (otherwise the concentrations on each side would be balanced by the solute crossing the membrane). If the volume of the solution on both sides of the membrane is the same, but the concentrations of solute are different, then there are different amounts of water, the solvent, on either side of the membrane.

Semipermeable membrane
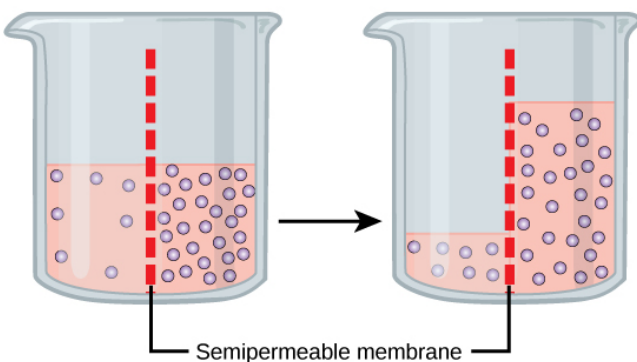
In osmosis, water always moves from an area of higher water concentration to one of lower concentration. In the diagram shown, the solute cannot pass through the selectively permeable membrane, but the water can.

To illustrate this, imagine two full glasses of water. One has a single teaspoon of sugar in it, whereas the second one contains one-quarter cup of sugar. If the total volume of the solutions in both cups is the same, which cup contains more water? Because the large amount of sugar in the second cup takes up much more space than the teaspoon of sugar in the first cup, the first cup has more water in it.

Returning to the beaker example, recall that it has a mixture of solutes on either side of the membrane. A principle of diffusion is that the molecules move around and will spread evenly throughout the medium if they can. However, only the material capable of getting through the membrane will diffuse through it. In this example, the solute cannot diffuse through the membrane, but the water can. Water has a concentration gradient in this system. Thus, water will diffuse down its concentration gradient, crossing the membrane to the side where it is less concentrated. This diffusion of water through the membrane—osmosis—will continue until the concentration gradient of water goes to zero or until the hydrostatic pressure of the water balances the osmotic pressure. Osmosis proceeds constantly in living systems.

Tonicity

Tonicity describes how an extracellular solution can change the volume of a cell by affecting osmosis. A solution's tonicity often directly correlates with the osmolarity of the solution. **Osmolarity** describes the total solute concentration of the solution. A solution with low osmolarity has a greater number of water molecules relative to the number of solute particles; a

solution with high osmolarity has fewer water molecules with respect to solute particles. In a situation in which solutions of two different osmolarities are separated by a membrane permeable to water, though not to the solute, water will move from the side of the membrane with lower osmolarity (and more water) to the side with higher osmolarity (and less water). This effect makes sense if you remember that the solute cannot move across the membrane, and thus the only component in the system that can move—the water—moves along its own concentration gradient. An important distinction that concerns living systems is that osmolarity measures the number of particles (which may be molecules) in a solution. Therefore, a solution that is cloudy with cells may have a lower osmolarity than a solution that is clear, if the second solution contains more dissolved molecules than there are cells.

Hypotonic Solutions

Three terms—hypotonic, isotonic, and hypertonic—are used to relate the osmolarity of a cell to the osmolarity of the extracellular fluid that contains the cells. In a **hypotonic** situation, the extracellular fluid has lower osmolarity than the fluid inside the cell, and water enters the cell. (In living systems, the point of reference is always the cytoplasm, so the prefix *hypo-* means that the extracellular fluid has a lower concentration of solutes, or a lower osmolarity, than the cell cytoplasm.) It also means that the extracellular fluid has a higher concentration of water in the solution than does the cell. In this situation, water will follow its concentration gradient and enter the cell.
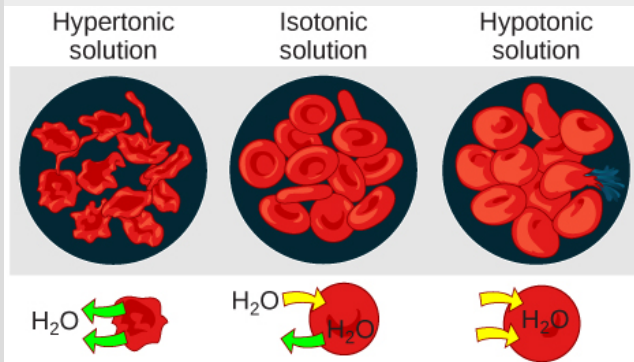
Hypertonic Solutions

As for a **hypertonic** solution, the prefix *hyper-* refers to the extracellular fluid having a higher osmolarity than the cell's cytoplasm; therefore, the fluid contains less water than the cell does. Because the cell has a relatively higher concentration of water, water will leave the cell.

Isotonic Solutions

In an **isotonic** solution, the extracellular fluid has the same osmolarity as the cell. If the osmolarity of the cell matches that of the extracellular fluid, there will be no net movement of water into or out of the cell, although water will still move in and out. Blood cells and plant cells in hypertonic, isotonic, and hypotonic solutions take on characteristic appearances ([link]).

Note:
Art Connection

Osmotic pressure changes the shape of red blood cells in hypertonic, isotonic, and hypotonic solutions. (credit: Mariana Ruiz Villareal)

A doctor injects a patient with what the doctor thinks is an isotonic saline solution. The patient dies, and an autopsy reveals that many red blood cells have been destroyed. Do you think the solution the doctor injected was really isotonic?

Note:
Link to Learning

Tonicity in Living Systems

In a hypotonic environment, water enters a cell, and the cell swells. In an isotonic condition, the relative concentrations of solute and solvent are equal on both sides of the membrane. There is no net water movement; therefore, there is no change in the size of the cell. In a hypertonic solution, water leaves a cell and the cell shrinks. If either the hypo- or hyper-condition goes to excess, the cell's functions become compromised, and the cell may be destroyed.

A red blood cell will burst, or lyse, when it swells beyond the plasma membrane's capability to expand. Remember, the membrane resembles a mosaic, with discrete spaces between the molecules composing it. If the cell swells, and the spaces between the lipids and proteins become too large, the cell will break apart.

In contrast, when excessive amounts of water leave a red blood cell, the cell shrinks, or crenates. This has the effect of concentrating the solutes left in the cell, making the cytosol denser and interfering with diffusion within the cell. The cell's ability to function will be compromised and may also result in the death of the cell.

Various living things have ways of controlling the effects of osmosis—a mechanism called osmoregulation. Some organisms, such as plants, fungi, bacteria, and some protists, have cell walls that surround the plasma membrane and prevent cell lysis in a hypotonic solution. The plasma membrane can only expand to the limit of the cell wall, so the cell will not

lyse. In fact, the cytoplasm in plants is always slightly hypertonic to the cellular environment, and water will always enter a cell if water is available. This inflow of water produces turgor pressure, which stiffens the cell walls of the plant ([link]). In nonwoody plants, turgor pressure supports the plant. Conversly, if the plant is not watered, the extracellular fluid will become hypertonic, causing water to leave the cell. In this condition, the cell does not shrink because the cell wall is not flexible. However, the cell membrane detaches from the wall and constricts the cytoplasm. This is called **plasmolysis**. Plants lose turgor pressure in this condition and wilt ([link]).
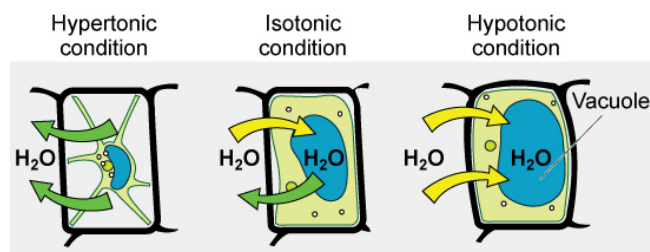
The turgor pressure within a plant cell depends on the tonicity of the solution that it is bathed in. (credit: modification of work by Mariana Ruiz Villareal)

Without adequate water, the plant on the left has lost turgor pressure, visible in its wilting; the turgor pressure is restored by watering it (right). (credit: Victor M. Vicente Selvas)

Tonicity is a concern for all living things. For example, paramecia and amoebas, which are protists that lack cell walls, have contractile vacuoles. This vesicle collects excess water from the cell and pumps it out, keeping the cell from lysing as it takes on water from its environment ([link]).

A paramecium's contractile vacuole, here visualized using bright field light microscopy at 480x magnification,

Many marine invertebrates have internal salt levels matched to their environments, making them isotonic with the water in which they live. Fish, however, must spend approximately five percent of their metabolic energy maintaining osmotic homeostasis. Freshwater fish live in an environment that is hypotonic to their cells. These fish actively take in salt through their gills and excrete diluted urine to rid themselves of excess water. Saltwater fish live in the reverse environment, which is hypertonic to their cells, and they secrete salt through their gills and excrete highly concentrated urine.

In vertebrates, the kidneys regulate the amount of water in the body. Osmoreceptors are specialized cells in the brain that monitor the concentration of solutes in the blood. If the levels of solutes increase beyond a certain range, a hormone is released that retards water loss through the kidney and dilutes the blood to safer levels. Animals also have high concentrations of albumin, which is produced by the liver, in their blood. This protein is too large to pass easily through plasma membranes and is a major factor in controlling the osmotic pressures applied to tissues.

Section Summary

The passive forms of transport, diffusion and osmosis, move materials of small molecular weight across membranes. Substances diffuse from areas of high concentration to areas of lower concentration, and this process continues until the substance is evenly distributed in a system. In solutions containing more than one substance, each type of molecule diffuses according to its own concentration gradient, independent of the diffusion of other substances. Many factors can affect the rate of diffusion, including concentration gradient, size of the particles that are diffusing, temperature of the system, and so on.

In living systems, diffusion of substances into and out of cells is mediated by the plasma membrane. Some materials diffuse readily through the membrane, but others are hindered, and their passage is made possible by specialized proteins, such as channels and transporters. The chemistry of living things occurs in aqueous solutions, and balancing the concentrations of those solutions is an ongoing problem. In living systems, diffusion of some substances would be slow or difficult without membrane proteins that facilitate transport.

Art Connections

Exercise:

Problem:

[link] A doctor injects a patient with what the doctor thinks is an isotonic saline solution. The patient dies, and an autopsy reveals that many red blood cells have been destroyed. Do you think the solution the doctor injected was really isotonic?

Solution:

[link] No, it must have been hypotonic as a hypotonic solution would cause water to enter the cells, thereby making them burst.

Review Questions

Exercise:

Problem: Water moves via osmosis _____.

  a. throughout the cytoplasm
  b. from an area with a high concentration of other solutes to a lower one
  c. from an area with a high concentration of water to one of lower concentration

d. from an area with a low concentration of water to one of higher concentration

---

Solution:

C

Exercise:

Problem:

The principal force driving movement in diffusion is the _____.

    a. temperature
    b. particle size
    c. concentration gradient
    d. membrane surface area

Solution:

C

Exercise:

Problem: What problem is faced by organisms that live in fresh water?

    a. Their bodies tend to take in too much water.
    b. They have no way of controlling their tonicity.
    c. Only salt water poses problems for animals that live in it.
    d. Their bodies tend to lose too much water to their environment.

Solution:

A

Free Response

Exercise:

Problem:

Discuss why the following affect the rate of diffusion: molecular size, temperature, solution density, and the distance that must be traveled.

Solution:

Heavy molecules move more slowly than lighter ones. It takes more energy in the medium to move them along. Increasing or decreasing temperature increases or decreases the energy in the medium, affecting molecular movement. The denser a solution is, the harder it is for molecules to move through it, causing diffusion to slow down due to friction. Living cells require a steady supply of nutrients and a steady rate of waste removal. If the distance these substances need to travel is too great, diffusion cannot move nutrients and waste materials efficiently to sustain life.

Exercise:

Problem: Why does water move through a membrane?

Solution:

Water moves through a membrane in osmosis because there is a concentration gradient across the membrane of solute and solvent. The solute cannot effectively move to balance the concentration on both sides of the membrane, so water moves to achieve this balance.

Exercise:

Problem:

Both of the regular intravenous solutions administered in medicine, normal saline and lactated Ringer's solution, are isotonic. Why is this important?

Solution:

Injection of isotonic solutions ensures that there will be no perturbation of the osmotic balance, and no water taken from tissues or added to them from the blood.

Glossary

aquaporin
> channel protein that allows water through the membrane at a very high rate

carrier protein
> membrane protein that moves a substance across the plasma membrane by changing its own shape

channel protein
> membrane protein that allows a substance to pass through its hollow core across the plasma membrane

concentration gradient
> area of high concentration adjacent to an area of low concentration

diffusion
> passive process of transport of low-molecular weight material according to its concentration gradient

facilitated transport
> process by which material moves down a concentration gradient (from high to low concentration) using integral membrane proteins

hypertonic
> situation in which extracellular fluid has a higher osmolarity than the fluid inside the cell, resulting in water moving out of the cell

hypotonic
> situation in which extracellular fluid has a lower osmolarity than the fluid inside the cell, resulting in water moving into the cell

isotonic
> situation in which the extracellular fluid has the same osmolarity as the fluid inside the cell, resulting in no net movement of water into or out of the cell

osmolarity
> total amount of substances dissolved in a specific amount of solution

osmosis
> transport of water through a semipermeable membrane according to the concentration gradient of water across the membrane that results from the presence of solute that cannot pass through the membrane

passive transport
> method of transporting material through a membrane that does not require energy

plasmolysis
> detaching of the cell membrane from the cell wall and constriction of the cell membrane when a plant cell is in a hypertonic solution

selectively permeable
> characteristic of a membrane that allows some substances through but not others

solute
> substance dissolved in a liquid to form a solution

tonicity
> amount of solute in a solution

transport protein
> membrane protein that facilitates passage of a substance across a membrane by binding it

Active Transport
By the end of this section, you will be able to:

- Understand how electrochemical gradients affect ions
- Distinguish between primary active transport and secondary active transport

Active transport mechanisms require the use of the cell's energy, usually in the form of adenosine triphosphate (ATP). If a substance must move into the cell against its concentration gradient—that is, if the concentration of the substance inside the cell is greater than its concentration in the extracellular fluid (and vice versa)—the cell must use energy to move the substance. Some active transport mechanisms move small-molecular weight materials, such as ions, through the membrane. Other mechanisms transport much larger molecules.

Electrochemical Gradient

We have discussed simple concentration gradients—differential concentrations of a substance across a space or a membrane—but in living systems, gradients are more complex. Because ions move into and out of cells and because cells contain proteins that do not move across the membrane and are mostly negatively charged, there is also an electrical gradient, a difference of charge, across the plasma membrane. The interior of living cells is electrically negative with respect to the extracellular fluid in which they are bathed, and at the same time, cells have higher concentrations of potassium (K^+) and lower concentrations of sodium (Na^+) than does the extracellular fluid. So in a living cell, the concentration gradient of Na^+ tends to drive it into the cell, and the electrical gradient of Na^+ (a positive ion) also tends to drive it inward to the negatively charged interior. The situation is more complex, however, for other elements such as potassium. The electrical gradient of K^+, a positive ion, also tends to drive it into the cell, but the concentration gradient of K^+ tends to drive K^+ *out* of the cell ([link]). The combined gradient of concentration and electrical charge that affects an ion is called its **electrochemical gradient**.
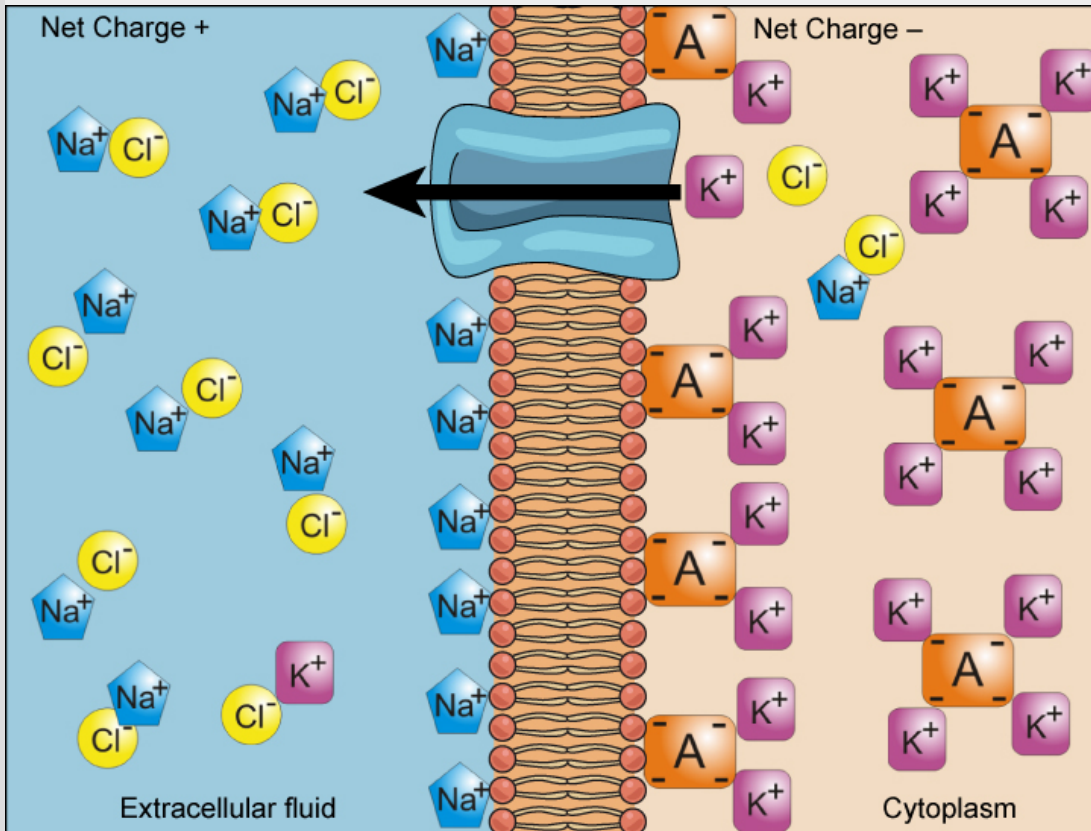
Electrochemical gradients arise from the combined effects of concentration gradients and electrical gradients. (credit: "Synaptitude"/Wikimedia Commons)

Injection of a potassium solution into a person's blood is lethal; this is used in capital punishment and euthanasia. Why do you think a potassium solution injection is lethal?

Moving Against a Gradient

To move substances against a concentration or electrochemical gradient, the cell must use energy. This energy is harvested from ATP generated through the cell's metabolism. Active transport mechanisms, collectively called

pumps, work against electrochemical gradients. Small substances constantly pass through plasma membranes. Active transport maintains concentrations of ions and other substances needed by living cells in the face of these passive movements. Much of a cell's supply of metabolic energy may be spent maintaining these processes. (Most of a red blood cell's metabolic energy is used to maintain the imbalance between exterior and interior sodium and potassium levels required by the cell.) Because active transport mechanisms depend on a cell's metabolism for energy, they are sensitive to many metabolic poisons that interfere with the supply of ATP.

Two mechanisms exist for the transport of small-molecular weight material and small molecules. **Primary active transport** moves ions across a membrane and creates a difference in charge across that membrane, which is directly dependent on ATP. **Secondary active transport** describes the movement of material that is due to the electrochemical gradient established by primary active transport that does not directly require ATP.

Carrier Proteins for Active Transport

An important membrane adaption for active transport is the presence of specific carrier proteins or pumps to facilitate movement: there are three types of these proteins or **transporters** ([link]). A **uniporter** carries one specific ion or molecule. A **symporter** carries two different ions or molecules, both in the same direction. An **antiporter** also carries two different ions or molecules, but in different directions. All of these transporters can also transport small, uncharged organic molecules like glucose. These three types of carrier proteins are also found in facilitated diffusion, but they do not require ATP to work in that process. Some examples of pumps for active transport are Na^+-K^+ ATPase, which carries sodium and potassium ions, and H^+-K^+ ATPase, which carries hydrogen and potassium ions. Both of these are antiporter carrier proteins. Two other carrier proteins are Ca^{2+} ATPase and H^+ ATPase, which carry only calcium and only hydrogen ions, respectively. Both are pumps.
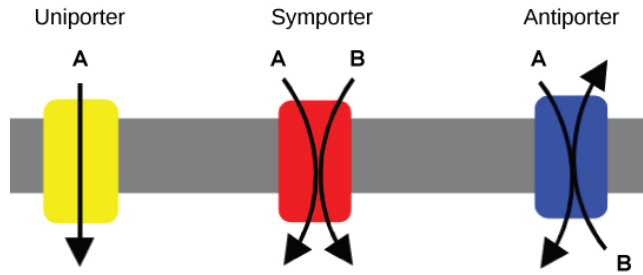
A uniporter carries one molecule or ion. A symporter carries two different molecules or ions, both in the same direction. An antiporter also carries two different molecules or ions, but in different directions. (credit: modification of work by "Lupask"/Wikimedia Commons)

Primary Active Transport

The primary active transport that functions with the active transport of sodium and potassium allows secondary active transport to occur. The second transport method is still considered active because it depends on the use of energy as does primary transport ([link]).
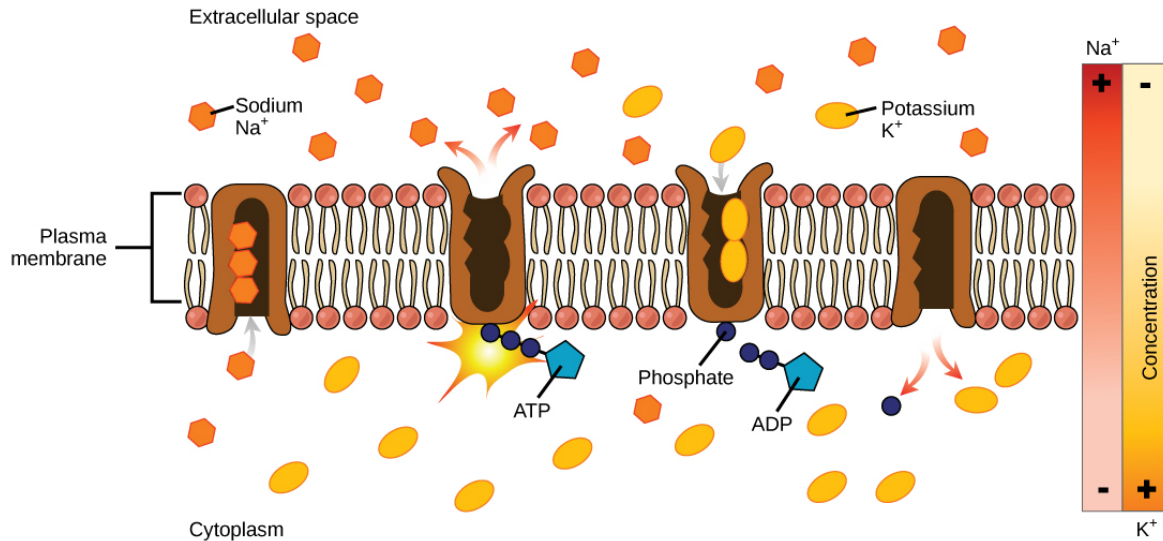
Primary active transport moves ions across a membrane, creating an electrochemical gradient (electrogenic transport). (credit: modification of work by Mariana Ruiz Villareal)

One of the most important pumps in animals cells is the sodium-potassium pump (Na$^+$-K$^+$ ATPase), which maintains the electrochemical gradient (and the correct concentrations of Na$^+$ and K$^+$) in living cells. The sodium-potassium pump moves K$^+$ into the cell while moving Na$^+$ out at the same time, at a ratio of three Na$^+$ for every two K$^+$ ions moved in. The Na$^+$-K$^+$ ATPase exists in two forms, depending on its orientation to the interior or exterior of the cell and its affinity for either sodium or potassium ions. The process consists of the following six steps.

1. With the enzyme oriented towards the interior of the cell, the carrier has a high affinity for sodium ions. Three ions bind to the protein.
2. ATP is hydrolyzed by the protein carrier and a low-energy phosphate group attaches to it.
3. As a result, the carrier changes shape and re-orients itself towards the exterior of the membrane. The protein's affinity for sodium decreases and the three sodium ions leave the carrier.
4. The shape change increases the carrier's affinity for potassium ions, and two such ions attach to the protein. Subsequently, the low-energy

phosphate group detaches from the carrier.

5. With the phosphate group removed and potassium ions attached, the carrier protein repositions itself towards the interior of the cell.
6. The carrier protein, in its new configuration, has a decreased affinity for potassium, and the two ions are released into the cytoplasm. The protein now has a higher affinity for sodium ions, and the process starts again.

Several things have happened as a result of this process. At this point, there are more sodium ions outside of the cell than inside and more potassium ions inside than out. For every three ions of sodium that move out, two ions of potassium move in. This results in the interior being slightly more negative relative to the exterior. This difference in charge is important in creating the conditions necessary for the secondary process. The sodium-potassium pump is, therefore, an **electrogenic pump** (a pump that creates a charge imbalance), creating an electrical imbalance across the membrane and contributing to the membrane potential.

Note:
Link to Learning

Watch this video to see a simulation of active transport in a sodium-potassium ATPase.

Secondary Active Transport (Co-transport)

Secondary active transport brings sodium ions, and possibly other compounds, into the cell. As sodium ion concentrations build outside of the plasma membrane because of the action of the primary active transport process, an electrochemical gradient is created. If a channel protein exists and is open, the sodium ions will be pulled through the membrane. This movement is used to transport other substances that can attach themselves to the transport protein through the membrane ([link]). Many amino acids, as well as glucose, enter a cell this way. This secondary process is also used to store high-energy hydrogen ions in the mitochondria of plant and animal cells for the production of ATP. The potential energy that accumulates in the stored hydrogen ions is translated into kinetic energy as the ions surge through the channel protein ATP synthase, and that energy is used to convert ADP into ATP.

Note:
Art Connection
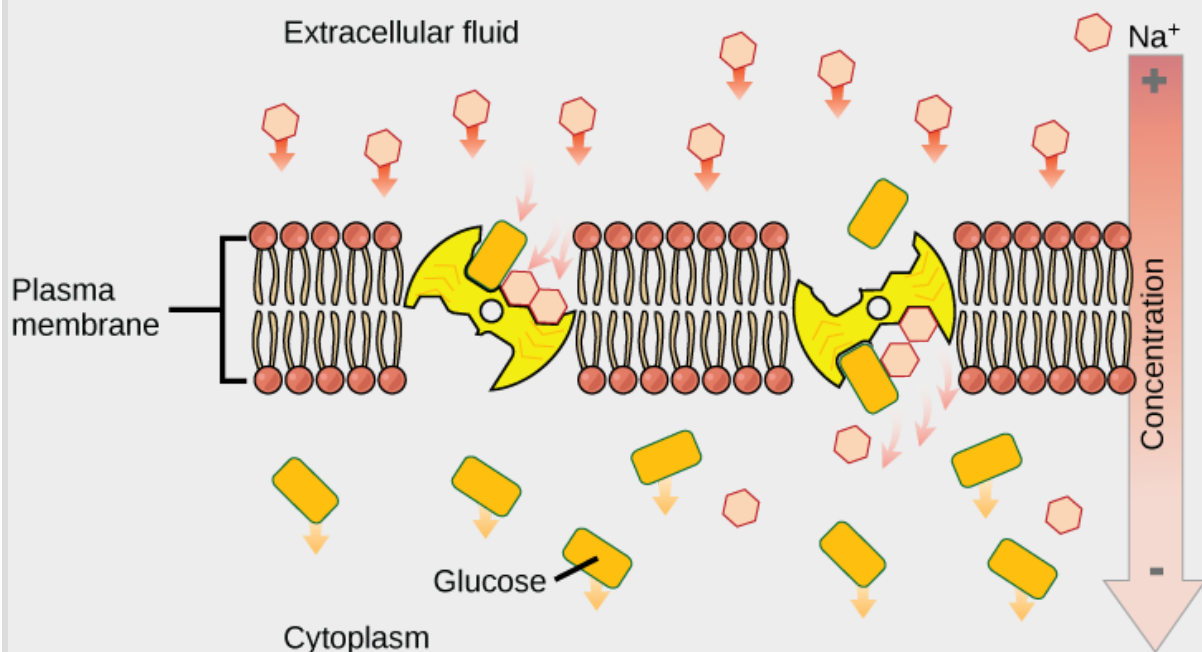
An electrochemical gradient, created by primary active transport, can move other substances against their concentration gradients, a process called co-transport or secondary active transport. (credit: modification of work by Mariana Ruiz Villareal)

If the pH outside the cell decreases, would you expect the amount of amino acids transported into the cell to increase or decrease?

Section Summary

The combined gradient that affects an ion includes its concentration gradient and its electrical gradient. A positive ion, for example, might tend to diffuse into a new area, down its concentration gradient, but if it is diffusing into an area of net positive charge, its diffusion will be hampered by its electrical gradient. When dealing with ions in aqueous solutions, a combination of the electrochemical and concentration gradients, rather than just the concentration gradient alone, must be considered. Living cells need certain substances that exist inside the cell in concentrations greater than they exist in the extracellular space. Moving substances up their electrochemical gradients requires energy from the cell. Active transport uses energy stored in ATP to fuel this transport. Active transport of small molecular-sized materials uses integral proteins in the cell membrane to move the materials: These proteins are analogous to pumps. Some pumps, which carry out primary active transport, couple directly with ATP to drive their action. In co-transport (or secondary active transport), energy from primary transport can be used to move another substance into the cell and up its concentration gradient.

Art Connections

Exercise:

Problem:

[link] Injection of a potassium solution into a person's blood is lethal; this is used in capital punishment and euthanasia. Why do you think a potassium solution injection is lethal?

Solution:

[link] Cells typically have a high concentration of potassium in the cytoplasm and are bathed in a high concentration of sodium. Injection of potassium dissipates this electrochemical gradient. In heart muscle, the sodium/potassium potential is responsible for transmitting the signal that causes the muscle to contract. When this potential is dissipated, the signal can't be transmitted, and the heart stops beating. Potassium injections are also used to stop the heart from beating during surgery.

Exercise:

Problem:

[link] If the pH outside the cell decreases, would you expect the amount of amino acids transported into the cell to increase or decrease?

Solution:

[link] A decrease in pH means an increase in positively charged H^+ ions, and an increase in the electrical gradient across the membrane. The transport of amino acids into the cell will increase.

Review Questions

Exercise:

Problem:

Active transport must function continuously because _____.

    a. plasma membranes wear out
    b. not all membranes are amphiphilic
    c. facilitated transport opposes active transport
    d. diffusion is constantly moving solutes in opposite directions

Solution:

D

Exercise:

Problem:

How does the sodium-potassium pump make the interior of the cell negatively charged?

    a. by expelling anions
    b. by pulling in anions
    c. by expelling more cations than are taken in
    d. by taking in and expelling an equal number of cations

Solution:

C

Exercise:

Problem:

What is the combination of an electrical gradient and a concentration gradient called?

    a. potential gradient
    b. electrical potential
    c. concentration potential
    d. electrochemical gradient

Solution:

D

Free Response

Exercise:

Problem:

Where does the cell get energy for active transport processes?

Solution:

The cell harvests energy from ATP produced by its own metabolism to power active transport processes, such as the activity of pumps.

Exercise:

Problem:

How does the sodium-potassium pump contribute to the net negative charge of the interior of the cell?

Solution:

The sodium-potassium pump forces out three (positive) Na^+ ions for every two (positive) K^+ ions it pumps in, thus the cell loses a positive charge at every cycle of the pump.

Glossary

active transport
> method of transporting material that requires energy

antiporter
> transporter that carries two ions or small molecules in different directions

electrochemical gradient
> gradient produced by the combined forces of an electrical gradient and a chemical gradient

electrogenic pump
> pump that creates a charge imbalance

primary active transport
    active transport that moves ions or small molecules across a membrane
    and may create a difference in charge across that membrane

pump
    active transport mechanism that works against electrochemical
    gradients

secondary active transport
    movement of material that is due to the electrochemical gradient
    established by primary active transport

symporter
    transporter that carries two different ions or small molecules, both in
    the same direction

transporter
    specific carrier proteins or pumps that facilitate movement

uniporter
    transporter that carries one specific ion or molecule

Bulk Transport
By the end of this section, you will be able to:

- Describe endocytosis, including phagocytosis, pinocytosis, and receptor-mediated endocytosis
- Understand the process of exocytosis

In addition to moving small ions and molecules through the membrane, cells also need to remove and take in larger molecules and particles (see [link] for examples). Some cells are even capable of engulfing entire unicellular microorganisms. You might have correctly hypothesized that the uptake and release of large particles by the cell requires energy. A large particle, however, cannot pass through the membrane, even with energy supplied by the cell.

Endocytosis

Endocytosis is a type of active transport that moves particles, such as large molecules, parts of cells, and even whole cells, into a cell. There are different variations of endocytosis, but all share a common characteristic: The plasma membrane of the cell invaginates, forming a pocket around the target particle. The pocket pinches off, resulting in the particle being contained in a newly created intracellular vesicle formed from the plasma membrane.

Phagocytosis

Phagocytosis (the condition of "cell eating") is the process by which large particles, such as cells or relatively large particles, are taken in by a cell. For example, when microorganisms invade the human body, a type of white blood cell called a neutrophil will remove the invaders through this process, surrounding and engulfing the microorganism, which is then destroyed by the neutrophil ([link]).

Phagocytosis

Large particle

Plasma
membrane

Vacuole
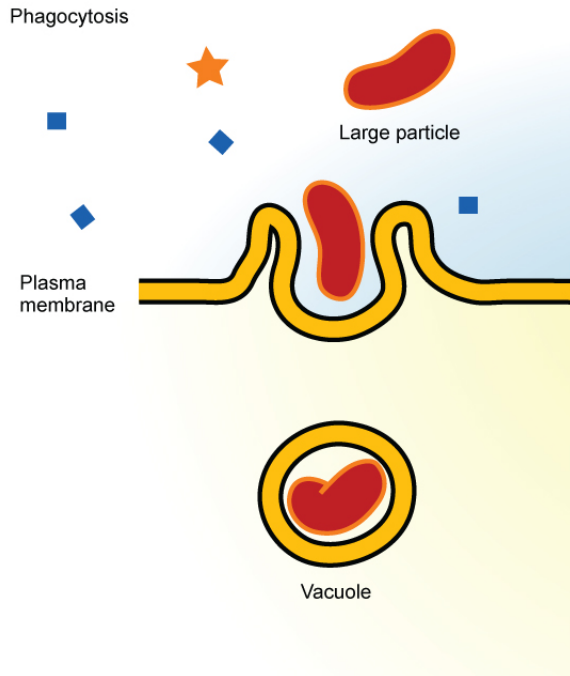
In phagocytosis, the cell
membrane surrounds the
particle and engulfs it. (credit:
Mariana Ruiz Villareal)

In preparation for phagocytosis, a portion of the inward-facing surface of the plasma membrane becomes coated with a protein called **clathrin**, which stabilizes this section of the membrane. The coated portion of the membrane then extends from the body of the cell and surrounds the particle, eventually enclosing it. Once the vesicle containing the particle is enclosed within the cell, the clathrin disengages from the membrane and the vesicle merges with a lysosome for the breakdown of the material in the newly formed compartment (endosome). When accessible nutrients from the degradation of the vesicular contents have been extracted, the newly formed endosome merges with the plasma membrane and releases its contents into the extracellular fluid. The endosomal membrane again becomes part of the plasma membrane.

Pinocytosis

A variation of endocytosis is called **pinocytosis**. This literally means "cell drinking" and was named at a time when the assumption was that the cell was purposefully taking in extracellular fluid. In reality, this is a process that takes in molecules, including water, which the cell needs from the extracellular fluid. Pinocytosis results in a much smaller vesicle than does phagocytosis, and the vesicle does not need to merge with a lysosome ([link]).

Pinocytosis

Vesicle
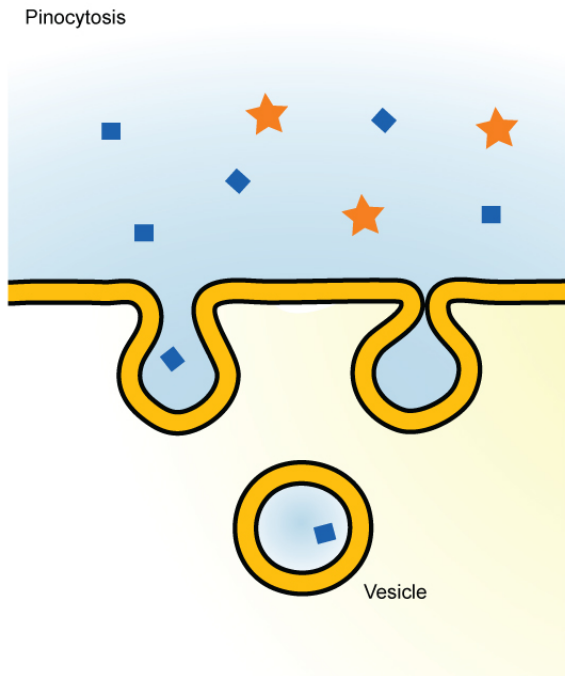
In pinocytosis, the cell membrane invaginates, surrounds a small volume of fluid, and pinches off. (credit: Mariana Ruiz Villareal)

A variation of pinocytosis is called **potocytosis**. This process uses a coating protein, called **caveolin**, on the cytoplasmic side of the plasma membrane,

which performs a similar function to clathrin. The cavities in the plasma membrane that form the vacuoles have membrane receptors and lipid rafts in addition to caveolin. The vacuoles or vesicles formed in caveolae (singular caveola) are smaller than those in pinocytosis. Potocytosis is used to bring small molecules into the cell and to transport these molecules through the cell for their release on the other side of the cell, a process called transcytosis.

Receptor-mediated Endocytosis

A targeted variation of endocytosis employs receptor proteins in the plasma membrane that have a specific binding affinity for certain substances ([link]).
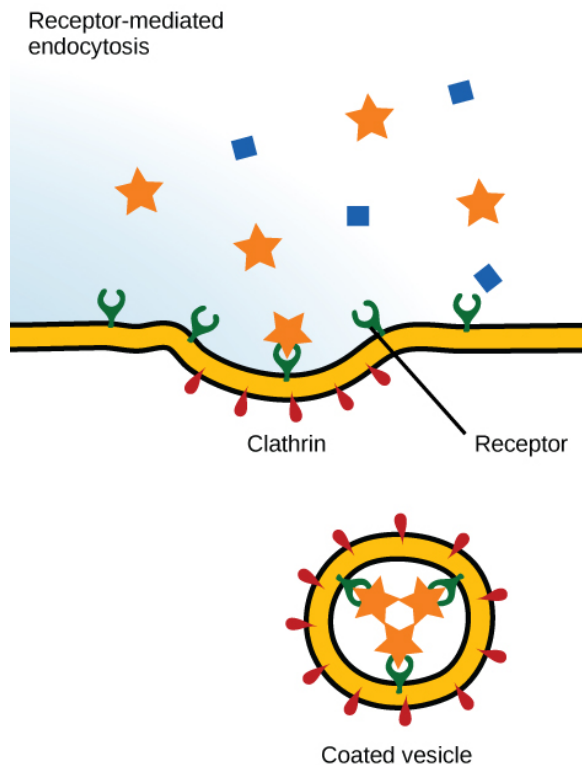
In receptor-mediated endocytosis, uptake of

substances by the cell is
targeted to a single type of
substance that binds to the
receptor on the external
surface of the cell membrane.
(credit: modification of work
by Mariana Ruiz Villareal)

In **receptor-mediated endocytosis**, as in phagocytosis, clathrin is attached to the cytoplasmic side of the plasma membrane. If uptake of a compound is dependent on receptor-mediated endocytosis and the process is ineffective, the material will not be removed from the tissue fluids or blood. Instead, it will stay in those fluids and increase in concentration. Some human diseases are caused by the failure of receptor-mediated endocytosis. For example, the form of cholesterol termed low-density lipoprotein or LDL (also referred to as "bad" cholesterol) is removed from the blood by receptor-mediated endocytosis. In the human genetic disease familial hypercholesterolemia, the LDL receptors are defective or missing entirely. People with this condition have life-threatening levels of cholesterol in their blood, because their cells cannot clear LDL particles from their blood.

Although receptor-mediated endocytosis is designed to bring specific substances that are normally found in the extracellular fluid into the cell, other substances may gain entry into the cell at the same site. Flu viruses, diphtheria, and cholera toxin all have sites that cross-react with normal receptor-binding sites and gain entry into cells.

Note:
Link to Learning

See receptor-mediated endocytosis in action, and click on different parts for a focused animation.

Exocytosis

The reverse process of moving material into a cell is the process of exocytosis. **Exocytosis** is the opposite of the processes discussed above in that its purpose is to expel material from the cell into the extracellular fluid. Waste material is enveloped in a membrane and fuses with the interior of the plasma membrane. This fusion opens the membranous envelope on the exterior of the cell, and the waste material is expelled into the extracellular space ([link]). Other examples of cells releasing molecules via exocytosis include the secretion of proteins of the extracellular matrix and secretion of neurotransmitters into the synaptic cleft by synaptic vesicles.

Exocytosis

Extracellular fluid

Cytoplasm
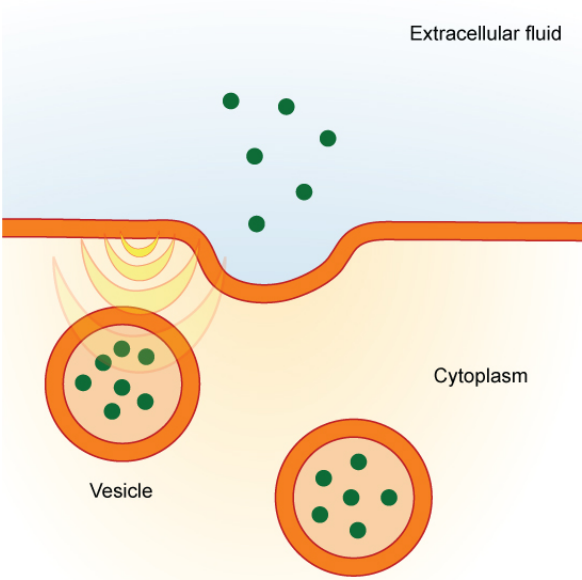
Vesicle

In exocytosis, vesicles
containing substances fuse
with the plasma membrane.
The contents are then released
to the exterior of the cell.
(credit: modification of work
by Mariana Ruiz Villareal)

Methods of Transport, Energy Requirements, and Types of Material Transported		
Transport Method	Active/Passive	Material Transported

Methods of Transport, Energy Requirements, and Types of Material Transported		
Transport Method	**Active/Passive**	**Material Transported**
Diffusion	Passive	Small-molecular weight material
Osmosis	Passive	Water
Facilitated transport/diffusion	Passive	Sodium, potassium, calcium, glucose
Primary active transport	Active	Sodium, potassium, calcium
Secondary active transport	Active	Amino acids, lactose
Phagocytosis	Active	Large macromolecules, whole cells, or cellular structures
Pinocytosis and potocytosis	Active	Small molecules (liquids/water)
Receptor-mediated endocytosis	Active	Large quantities of macromolecules

Section Summary

Active transport methods require the direct use of ATP to fuel the transport. Large particles, such as macromolecules, parts of cells, or whole cells, can be engulfed by other cells in a process called phagocytosis. In phagocytosis,

a portion of the membrane invaginates and flows around the particle, eventually pinching off and leaving the particle entirely enclosed by an envelope of plasma membrane. Vesicle contents are broken down by the cell, with the particles either used as food or dispatched. Pinocytosis is a similar process on a smaller scale. The plasma membrane invaginates and pinches off, producing a small envelope of fluid from outside the cell. Pinocytosis imports substances that the cell needs from the extracellular fluid. The cell expels waste in a similar but reverse manner: it pushes a membranous vacuole to the plasma membrane, allowing the vacuole to fuse with the membrane and incorporate itself into the membrane structure, releasing its contents to the exterior.

Review Questions

Exercise:

Problem: What happens to the membrane of a vesicle after exocytosis?

   a. It leaves the cell.
   b. It is disassembled by the cell.
   c. It fuses with and becomes part of the plasma membrane.
   d. It is used again in another exocytosis event.

Solution:

C

Exercise:
Problem:

Which transport mechanism can bring whole cells into a cell?

   a. pinocytosis
   b. phagocytosis
   c. facilitated transport
   d. primary active transport

Solution:

B

Exercise:

Problem:

In what important way does receptor-mediated endocytosis differ from phagocytosis?

    a. It transports only small amounts of fluid.
    b. It does not involve the pinching off of membrane.
    c. It brings in only a specifically targeted substance.
    d. It brings substances into the cell, while phagocytosis removes substances.

Solution:

C

Free Response

Exercise:

Problem:

Why is it important that there are different types of proteins in plasma membranes for the transport of materials into and out of a cell?

Solution:

The proteins allow a cell to select what compound will be transported, meeting the needs of the cell and not bringing in anything else.

Exercise:

Problem:

Why do ions have a difficult time getting through plasma membranes despite their small size?

Solution:

Ions are charged, and consequently, they are hydrophilic and cannot associate with the lipid portion of the membrane. Ions must be transported by carrier proteins or ion channels.

Glossary

caveolin
> protein that coats the cytoplasmic side of the plasma membrane and participates in the process of liquid update by potocytosis

clathrin
> protein that coats the inward-facing surface of the plasma membrane and assists in the formation of specialized structures, like coated pits, for phagocytosis

endocytosis
> type of active transport that moves substances, including fluids and particles, into a cell

exocytosis
> process of passing bulk material out of a cell

pinocytosis
> a variation of endocytosis that imports macromolecules that the cell needs from the extracellular fluid

potocytosis
> variation of pinocytosis that uses a different coating protein (caveolin) on the cytoplasmic side of the plasma membrane

receptor-mediated endocytosis

      variation of endocytosis that involves the use of specific binding
      proteins in the plasma membrane for specific molecules or particles,
      and clathrin-coated pits that become clathrin-coated vesicles

Introduction
class="introduction"

A hummingbird needs energy to maintain prolonged periods of flight. The bird obtains its energy from taking in food and transforming the nutrients into energy through a series of biochemical reactions. The flight muscles in birds are extremely efficient in energy production. (credit: modification of work by Cory Zanker)

Virtually every task performed by living organisms requires energy. Energy is needed to perform heavy labor and exercise, but humans also use a great deal of energy while thinking, and even during sleep. In fact, the living cells of every organism constantly use energy. Nutrients and other molecules are imported, metabolized (broken down) and possibly synthesized into new molecules, modified if needed, transported around the cell, and may be distributed to the entire organism. For example, the large proteins that make up muscles are actively built from smaller molecules. Complex carbohydrates are broken down into simple sugars that the cell uses for energy. Just as energy is required to both build and demolish a building, energy is required for both the synthesis and breakdown of molecules. Additionally, signaling molecules such as hormones and neurotransmitters are transported between cells. Pathogenic bacteria and viruses are ingested and broken down by cells. Cells must also export waste and toxins to stay healthy, and many cells must swim or move surrounding materials via the beating motion of cellular appendages like cilia and flagella.

The cellular processes listed above require a steady supply of energy. From where, and in what form, does this energy come? How do living cells obtain energy, and how do they use it? This chapter will discuss different forms of energy and the physical laws that govern energy transfer. This chapter will

also describe how cells use energy and replenish it, and how chemical reactions in the cell are performed with great efficiency.

Energy and Metabolism
By the end of this section, you will be able to:

- Explain what metabolic pathways are and describe the two major types of metabolic pathways
- Discuss how chemical reactions play a role in energy transfer

Scientists use the term **bioenergetics** to discuss the concept of energy flow ([link]) through living systems, such as cells. Cellular processes such as the building and breaking down of complex molecules occur through stepwise chemical reactions. Some of these chemical reactions are spontaneous and release energy, whereas others require energy to proceed. Just as living things must continually consume food to replenish what has been used, cells must continually produce more energy to replenish that used by the many energy-requiring chemical reactions that constantly take place. All of the chemical reactions that take place inside cells, including those that use energy and those that release energy, are the cell's **metabolism**.
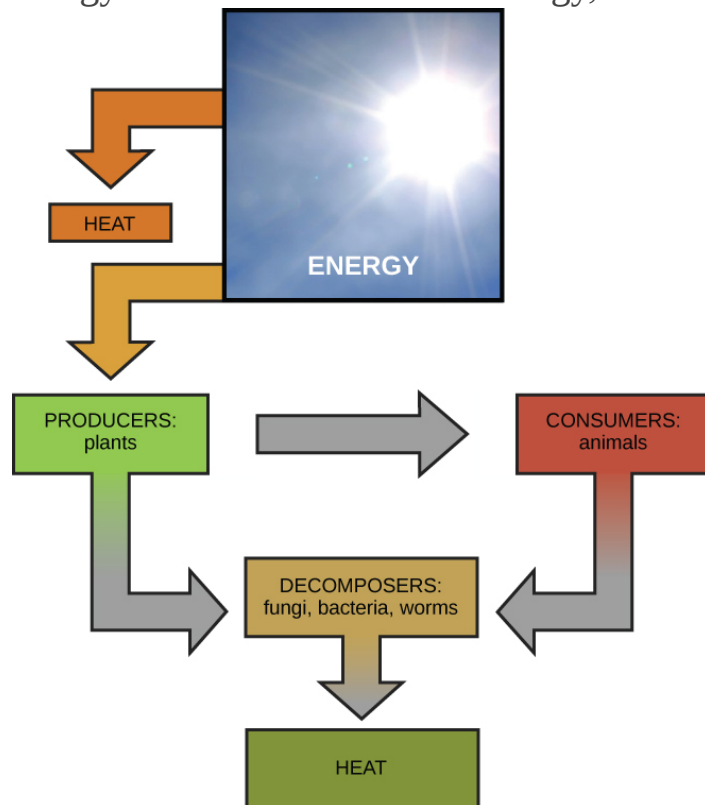
Most life forms on earth get their
energy from the sun. Plants use

photosynthesis to capture sunlight, and herbivores eat those plants to obtain energy. Carnivores eat the herbivores, and decomposers digest plant and animal matter.

Metabolism of Carbohydrates

The metabolism of sugar (a simple carbohydrate) is a classic example of the many cellular processes that use and produce energy. Living things consume sugar as a major energy source, because sugar molecules have a great deal of energy stored within their bonds. The breakdown of glucose, a simple sugar, is described by the equation:

Equation:

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + \text{energy}$$

Carbohydrates that are consumed have their origins in photosynthesizing organisms like plants ([link]). During photosynthesis, plants use the energy of sunlight to convert carbon dioxide gas (CO_2) into sugar molecules, like glucose ($C_6H_{12}O_6$). Because this process involves synthesizing a larger, energy-storing molecule, it requires an input of energy to proceed. The synthesis of glucose is described by this equation (notice that it is the reverse of the previous equation):

Equation:

$$6CO_2 + 6H_2O + \text{energy} \rightarrow C_6H_{12}O_6 + 6O_2$$

During the chemical reactions of photosynthesis, energy is provided in the form of a very high-energy molecule called ATP, or adenosine triphosphate, which is the primary energy currency of all cells. Just as the dollar is used as currency to buy goods, cells use molecules of ATP as energy currency to perform immediate work. The sugar (glucose) is stored as starch or

glycogen. Energy-storing polymers like these are broken down into glucose to supply molecules of ATP.

Solar energy is required to synthesize a molecule of glucose during the reactions of photosynthesis. In photosynthesis, light energy from the sun is initially transformed into chemical energy that is temporally stored in the energy carrier molecules ATP and NADPH (nicotinamide adenine dinucleotide phosphate). The stored energy in ATP and NADPH is then used later in photosynthesis to build one molecule of glucose from six molecules of CO_2. This process is analogous to eating breakfast in the morning to acquire energy for your body that can be used later in the day. Under ideal conditions, energy from 18 molecules of ATP is required to synthesize one molecule of glucose during the reactions of photosynthesis. Glucose molecules can also be combined with and converted into other types of sugars. When sugars are consumed, molecules of glucose eventually make their way into each living cell of the organism. Inside the cell, each sugar molecule is broken down through a complex series of chemical reactions. The goal of these reactions is to harvest the energy stored inside the sugar molecules. The harvested energy is used to make high-energy ATP molecules, which can be used to perform work, powering many chemical reactions in the cell. The amount of energy needed to make one molecule of glucose from six molecules of carbon dioxide is 18 molecules of ATP and 12 molecules of NADPH (each one of which is energetically equivalent to three molecules of ATP), or a total of 54 molecule equivalents required for the synthesis of one molecule of glucose. This process is a fundamental and efficient way for cells to generate the molecular energy that they require.

Plants, like this oak tree and acorn, use energy from sunlight to make sugar and other organic molecules. Both plants and animals (like this squirrel) use cellular respiration to derive energy from the organic molecules originally produced by plants. (credit "acorn": modification of work by Noel Reynolds; credit "squirrel": modification of work by Dawn Huczek)

Metabolic Pathways

The processes of making and breaking down sugar molecules illustrate two types of metabolic pathways. A metabolic pathway is a series of interconnected biochemical reactions that convert a substrate molecule or molecules, step-by-step, through a series of metabolic intermediates, eventually yielding a final product or products. In the case of sugar metabolism, the first metabolic pathway synthesized sugar from smaller molecules, and the other pathway broke sugar down into smaller molecules. These two opposite processes—the first requiring energy and the second producing energy—are referred to as anabolic (building) and catabolic (breaking down) pathways, respectively. Consequently, metabolism is composed of building (anabolism) and degradation (catabolism).

Note:
Evolution Connection
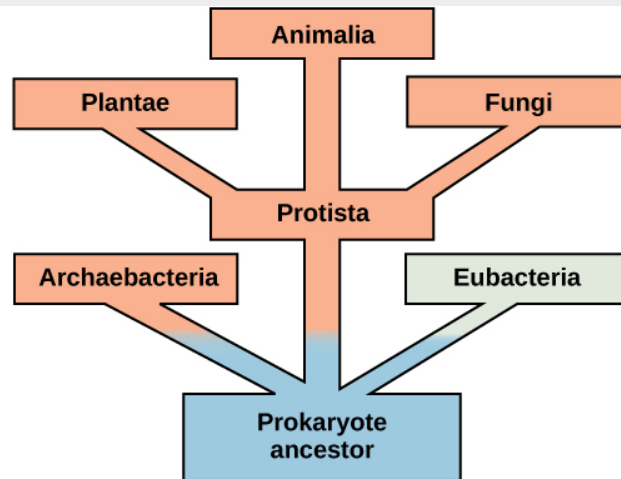
This tree shows the evolution of the various branches of life. The vertical dimension is time. Early life forms, in blue, used anaerobic metabolism to obtain energy from their surroundings.

Evolution of Metabolic Pathways

There is more to the complexity of metabolism than understanding the metabolic pathways alone. Metabolic complexity varies from organism to organism. Photosynthesis is the primary pathway in which photosynthetic organisms like plants (the majority of global synthesis is done by planktonic algae) harvest the sun's energy and convert it into carbohydrates. The by-product of photosynthesis is oxygen, required by some cells to carry out cellular respiration. During cellular respiration, oxygen aids in the catabolic breakdown of carbon compounds, like carbohydrates. Among the products of this catabolism are CO_2 and ATP. In addition, some eukaryotes perform catabolic processes without oxygen (fermentation); that is, they perform or use anaerobic metabolism. Organisms probably evolved anaerobic metabolism to survive (living organisms came into existence about 3.8 billion years ago, when the atmosphere lacked oxygen). Despite the differences between organisms and the complexity of metabolism, researchers have found that all branches of life share some of the same metabolic pathways, suggesting that all

organisms evolved from the same ancient common ancestor ([link]). Evidence indicates that over time, the pathways diverged, adding specialized enzymes to allow organisms to better adapt to their environment, thus increasing their chance to survive. However, the underlying principle remains that all organisms must harvest energy from their environment and convert it to ATP to carry out cellular functions.
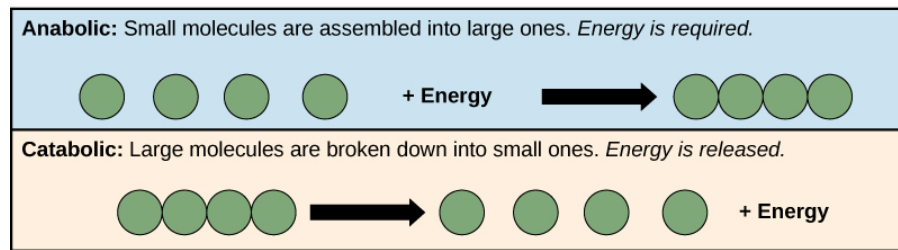
Anabolic and Catabolic Pathways

Anabolic pathways require an input of energy to synthesize complex molecules from simpler ones. Synthesizing sugar from CO_2 is one example. Other examples are the synthesis of large proteins from amino acid building blocks, and the synthesis of new DNA strands from nucleic acid building blocks. These biosynthetic processes are critical to the life of the cell, take place constantly, and demand energy provided by ATP and other high-energy molecules like NADH (nicotinamide adenine dinucleotide) and NADPH ([link]).

ATP is an important molecule for cells to have in sufficient supply at all times. The breakdown of sugars illustrates how a single molecule of glucose can store enough energy to make a great deal of ATP, 36 to 38 molecules. This is a **catabolic** pathway. Catabolic pathways involve the degradation (or breakdown) of complex molecules into simpler ones. Molecular energy stored in the bonds of complex molecules is released in catabolic pathways and harvested in such a way that it can be used to produce ATP. Other energy-storing molecules, such as fats, are also broken down through similar catabolic reactions to release energy and make ATP ([link]).

It is important to know that the chemical reactions of metabolic pathways don't take place spontaneously. Each reaction step is facilitated, or catalyzed, by a protein called an enzyme. Enzymes are important for catalyzing all types of biological reactions—those that require energy as well as those that release energy.

Metabolic pathways

Anabolic: Small molecules are assembled into large ones. *Energy is required.*

+ Energy

Catabolic: Large molecules are broken down into small ones. *Energy is released.*

+ Energy

Anabolic pathways are those that require energy to synthesize larger molecules. Catabolic pathways are those that generate energy by breaking down larger molecules. Both types of pathways are required for maintaining the cell's energy balance.

Section Summary

Cells perform the functions of life through various chemical reactions. A cell's metabolism refers to the chemical reactions that take place within it. There are metabolic reactions that involve the breaking down of complex chemicals into simpler ones, such as the breakdown of large macromolecules. This process is referred to as catabolism, and such reactions are associated with a release of energy. On the other end of the spectrum, anabolism refers to metabolic processes that build complex molecules out of simpler ones, such as the synthesis of macromolecules. Anabolic processes require energy. Glucose synthesis and glucose breakdown are examples of anabolic and catabolic pathways, respectively.

Multiple Choice

Exercise:

Problem:

Energy is stored long-term in the bonds of _____ and used short-term to perform work from a(n) _____ molecule.

a. ATP : glucose
    b. an anabolic molecule : catabolic molecule
    c. glucose : ATP
    d. a catabolic molecule : anabolic molecule

Solution:

C

Exercise:

Problem:

DNA replication involves unwinding two strands of parent DNA, copying each strand to synthesize complementary strands, and releasing the parent and daughter DNA. Which of the following accurately describes this process?

    a. This is an anabolic process
    b. This is a catabolic process
    c. This is both anabolic and catabolic
    d. This is a metabolic process but is neither anabolic nor catabolic

---

Solution:

A

Free Response

Exercise:

Problem:

Does physical exercise involve anabolic and/or catabolic processes? Give evidence for your answer.

Solution:

Physical exercise involves both anabolic and catabolic processes. Body cells break down sugars to provide ATP to do the work necessary for exercise, such as muscle contractions. This is catabolism. Muscle cells also must repair muscle tissue damaged by exercise by building new muscle. This is anabolism.

Exercise:

Problem:

Name two different cellular functions that require energy that parallel human energy-requiring functions.

Solution:

Energy is required for cellular motion, through beating of cilia or flagella, as well as human motion, produced by muscle contraction. Cells also need energy to perform digestion, as humans require energy to digest food.

Glossary

anabolic
    (also, anabolism) pathways that require an input of energy to synthesize complex molecules from simpler ones

bioenergetics
    study of energy flowing through living systems

catabolic
    (also, catabolism) pathways in which complex molecules are broken down into simpler ones

metabolism
    all the chemical reactions that take place inside cells, including anabolism and catabolism

Potential, Kinetic, Free, and Activation Energy
By the end of this section, you will be able to:

- Define "energy"
- Explain the difference between kinetic and potential energy
- Discuss the concepts of free energy and activation energy
- Describe endergonic and exergonic reactions

Energy is defined as the ability to do work. As you've learned, energy exists in different forms. For example, electrical energy, light energy, and heat energy are all different types of energy. While these are all familiar types of energy that one can see or feel, there is another type of energy that is much less tangible. This energy is associated with something as simple as an object held above the ground. In order to appreciate the way energy flows into and out of biological systems, it is important to understand more about the different types of energy that exist in the physical world.

Types of Energy

When an object is in motion, there is energy associated with that object. In the example of an airplane in flight, there is a great deal of energy associated with the motion of the airplane. This is because moving objects are capable of enacting a change, or doing work. Think of a wrecking ball. Even a slow-moving wrecking ball can do a great deal of damage to other objects. However, a wrecking ball that is not in motion is incapable of performing work. Energy associated with objects in motion is called **kinetic energy**. A speeding bullet, a walking person, the rapid movement of molecules in the air (which produces heat), and electromagnetic radiation like light all have kinetic energy.

Now what if that same motionless wrecking ball is lifted two stories above a car with a crane? If the suspended wrecking ball is unmoving, is there energy associated with it? The answer is yes. The suspended wrecking ball has energy associated with it that is fundamentally different from the kinetic energy of objects in motion. This form of energy results from the fact that there is the *potential* for the wrecking ball to do work. If it is released, indeed it would do work. Because this type of energy refers to the potential

to do work, it is called **potential energy**. Objects transfer their energy between kinetic and potential in the following way: As the wrecking ball hangs motionless, it has 0 kinetic and 100 percent potential energy. Once it is released, its kinetic energy begins to increase because it builds speed due to gravity. At the same time, as it nears the ground, it loses potential energy. Somewhere mid-fall it has 50 percent kinetic and 50 percent potential energy. Just before it hits the ground, the ball has nearly lost its potential energy and has near-maximal kinetic energy. Other examples of potential energy include the energy of water held behind a dam ([link]), or a person about to skydive out of an airplane.

Water behind a dam has potential energy. Moving water, such as in a waterfall or a rapidly flowing river, has kinetic energy. (credit "dam": modification of work by "Pascal"/Flickr; credit "waterfall": modification of work by Frank Gualtieri)

Potential energy is not only associated with the location of matter (such as a child sitting on a tree branch), but also with the structure of matter. A spring on the ground has potential energy if it is compressed; so does a rubber band that is pulled taut. The very existence of living cells relies heavily on structural potential energy. On a chemical level, the bonds that hold the atoms of molecules together have potential energy. Remember that anabolic

cellular pathways require energy to synthesize complex molecules from simpler ones, and catabolic pathways release energy when complex molecules are broken down. The fact that energy can be released by the breakdown of certain chemical bonds implies that those bonds have potential energy. In fact, there is potential energy stored within the bonds of all the food molecules we eat, which is eventually harnessed for use. This is because these bonds can release energy when broken. The type of potential energy that exists within chemical bonds, and is released when those bonds are broken, is called **chemical energy** ([link]). Chemical energy is responsible for providing living cells with energy from food. The release of energy is brought about by breaking the molecular bonds within fuel molecules.
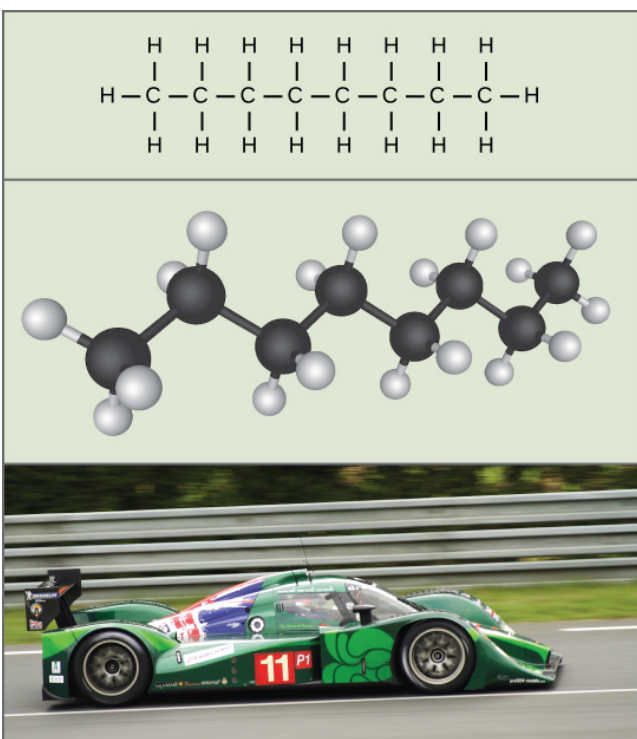
The molecules in gasoline (octane, the chemical formula shown) contain chemical energy within the chemical bonds. This energy is transformed into kinetic energy

that allows a car to race on a racetrack. (credit "car": modification of work by Russell Trow)

Free Energy

After learning that chemical reactions release energy when energy-storing bonds are broken, an important next question is how is the energy associated with chemical reactions quantified and expressed? How can the energy released from one reaction be compared to that of another reaction? A measurement of **free energy** is used to quantitate these energy transfers. Free energy is called Gibbs free energy (abbreviated with the letter G) after Josiah Willard Gibbs, the scientist who developed the measurement. Recall that according to the second law of thermodynamics, all energy transfers involve the loss of some amount of energy in an unusable form such as heat, resulting in entropy. Gibbs free energy specifically refers to the energy associated with a chemical reaction that is available after entropy is

accounted for. In other words, Gibbs free energy is usable energy, or energy that is available to do work.

Every chemical reaction involves a change in free energy, called delta G (ΔG). The change in free energy can be calculated for any system that undergoes such a change, such as a chemical reaction. To calculate ΔG, subtract the amount of energy lost to entropy (denoted as ΔS) from the total energy change of the system. This total energy change in the system is called **enthalpy** and is denoted as ΔH . The formula for calculating ΔG is as follows, where the symbol T refers to absolute temperature in Kelvin (degrees Celsius + 273):
Equation:

$$\Delta G = \Delta H - T \Delta S$$

The standard free energy change of a chemical reaction is expressed as an amount of energy per mole of the reaction product (either in kilojoules or kilocalories, kJ/mol or kcal/mol; 1 kJ = 0.239 kcal) under standard pH, temperature, and pressure conditions. Standard pH, temperature, and pressure conditions are generally calculated at pH 7.0 in biological systems, 25 degrees Celsius, and 100 kilopascals (1 atm pressure), respectively. It is important to note that cellular conditions vary considerably from these standard conditions, and so standard calculated ΔG values for biological reactions will be different inside the cell.

Endergonic Reactions and Exergonic Reactions

If energy is released during a chemical reaction, then the resulting value from the above equation will be a negative number. In other words, reactions that release energy have a ΔG < 0. A negative ΔG also means that the products of the reaction have less free energy than the reactants, because they gave off some free energy during the reaction. Reactions that have a negative ΔG and consequently release free energy are called **exergonic reactions**. Think: *ex*ergonic means energy is *ex*iting the system. These reactions are also referred to as spontaneous reactions, because they can

occur without the addition of energy into the system. Understanding which chemical reactions are spontaneous and release free energy is extremely useful for biologists, because these reactions can be harnessed to perform work inside the cell. An important distinction must be drawn between the term spontaneous and the idea of a chemical reaction that occurs immediately. Contrary to the everyday use of the term, a spontaneous reaction is not one that suddenly or quickly occurs. The rusting of iron is an example of a spontaneous reaction that occurs slowly, little by little, over time.

If a chemical reaction requires an input of energy rather than releasing energy, then the ΔG for that reaction will be a positive value. In this case, the products have more free energy than the reactants. Thus, the products of these reactions can be thought of as energy-storing molecules. These chemical reactions are called **endergonic reactions**, and they are non-spontaneous. An endergonic reaction will not take place on its own without the addition of free energy.

Let's revisit the example of the synthesis and breakdown of the food molecule, glucose. Remember that the building of complex molecules, such as sugars, from simpler ones is an anabolic process and requires energy. Therefore, the chemical reactions involved in anabolic processes are endergonic reactions. On the other hand, the catabolic process of breaking sugar down into simpler molecules releases energy in a series of exergonic reactions. Like the example of rust above, the breakdown of sugar involves spontaneous reactions, but these reactions don't occur instantaneously. [link] shows some other examples of endergonic and exergonic reactions. Later sections will provide more information about what else is required to make even spontaneous reactions happen more efficiently.

Note:
Art Connection

(a)

(b)

(c)

(d)

Shown are some examples of endergonic processes (ones that require energy) and exergonic processes (ones that release energy). These include (a) a compost pile decomposing, (b) a chick hatching from a fertilized egg, (c) sand art being destroyed, and (d) a ball rolling down a hill. (credit a: modification of work by Natalie Maynor; credit b: modification of work by USDA; credit c: modification of work by "Athlex"/Flickr; credit d: modification of work by Harry Malsch)

Look at each of the processes shown, and decide if it is endergonic or exergonic. In each case, does enthalpy increase or decrease, and does entropy increase or decrease?

An important concept in the study of metabolism and energy is that of chemical equilibrium. Most chemical reactions are reversible. They can

proceed in both directions, releasing energy into their environment in one direction, and absorbing it from the environment in the other direction ([link]). The same is true for the chemical reactions involved in cell metabolism, such as the breaking down and building up of proteins into and from individual amino acids, respectively. Reactants within a closed system will undergo chemical reactions in both directions until a state of equilibrium is reached. This state of equilibrium is one of the lowest possible free energy and a state of maximal entropy. Energy must be put into the system to push the reactants and products away from a state of equilibrium. Either reactants or products must be added, removed, or changed. If a cell were a closed system, its chemical reactions would reach equilibrium, and it would die because there would be insufficient free energy left to perform the work needed to maintain life. In a living cell, chemical reactions are constantly moving towards equilibrium, but never reach it. This is because a living cell is an open system. Materials pass in and out, the cell recycles the products of certain chemical reactions into other reactions, and chemical equilibrium is never reached. In this way, living organisms are in a constant energy-requiring, uphill battle against equilibrium and entropy. This constant supply of energy ultimately comes from sunlight, which is used to produce nutrients in the process of photosynthesis.
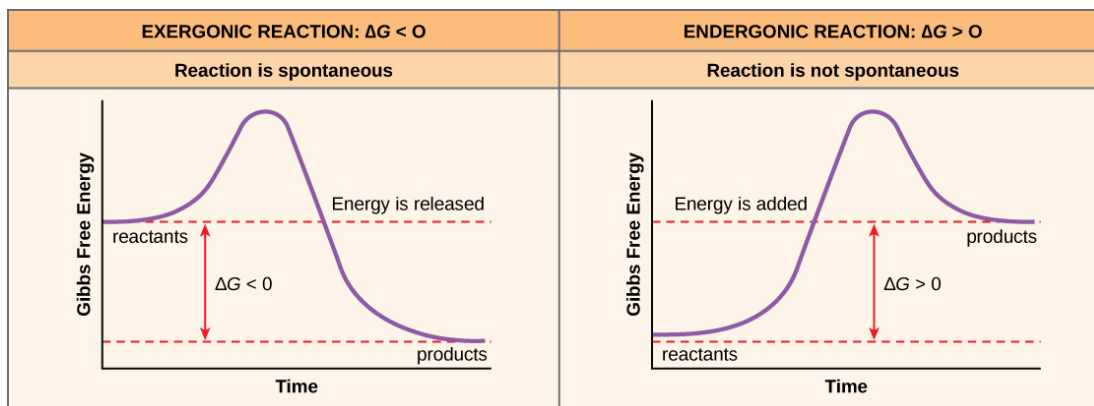
Exergonic and endergonic reactions result in changes in Gibbs free energy. Exergonic reactions release energy; endergonic reactions require energy to proceed.

Activation Energy

There is another important concept that must be considered regarding endergonic and exergonic reactions. Even exergonic reactions require a small amount of energy input to get going before they can proceed with their energy-releasing steps. These reactions have a net release of energy, but still require some energy in the beginning. This small amount of energy input necessary for all chemical reactions to occur is called the **activation energy** (or free energy of activation) and is abbreviated E_A ([link]).

Why would an energy-releasing, negative ΔG reaction actually require some energy to proceed? The reason lies in the steps that take place during a chemical reaction. During chemical reactions, certain chemical bonds are broken and new ones are formed. For example, when a glucose molecule is broken down, bonds between the carbon atoms of the molecule are broken. Since these are energy-storing bonds, they release energy when broken. However, to get them into a state that allows the bonds to break, the molecule must be somewhat contorted. A small energy input is required to achieve this contorted state. This contorted state is called the **transition state**, and it is a high-energy, unstable state. For this reason, reactant molecules don't last long in their transition state, but very quickly proceed to the next steps of the chemical reaction. Free energy diagrams illustrate the energy profiles for a given reaction. Whether the reaction is exergonic or endergonic determines whether the products in the diagram will exist at a lower or higher energy state than both the reactants and the products. However, regardless of this measure, the transition state of the reaction exists at a higher energy state than the reactants, and thus, E_A is always positive.

Note:
Link to Learning

Where does the activation energy required by chemical reactants come from? The source of the activation energy needed to push reactions forward is typically heat energy from the surroundings. **Heat energy** (the total bond energy of reactants or products in a chemical reaction) speeds up the motion of molecules, increasing the frequency and force with which they collide; it also moves atoms and bonds within the molecule slightly, helping them reach their transition state. For this reason, heating up a system will cause chemical reactants within that system to react more frequently. Increasing the pressure on a system has the same effect. Once reactants have absorbed enough heat energy from their surroundings to reach the transition state, the reaction will proceed.

The activation energy of a particular reaction determines the rate at which it will proceed. The higher the activation energy, the slower the chemical reaction will be. The example of iron rusting illustrates an inherently slow reaction. This reaction occurs slowly over time because of its high E_A. Additionally, the burning of many fuels, which is strongly exergonic, will take place at a negligible rate unless their activation energy is overcome by sufficient heat from a spark. Once they begin to burn, however, the chemical reactions release enough heat to continue the burning process, supplying the activation energy for surrounding fuel molecules. Like these reactions outside of cells, the activation energy for most cellular reactions is too high for heat energy to overcome at efficient rates. In other words, in order for important cellular reactions to occur at appreciable rates (number of reactions per unit time), their activation energies must be lowered ([[link]](link)); this is referred to as catalysis. This is a very good thing as far as

living cells are concerned. Important macromolecules, such as proteins, DNA, and RNA, store considerable energy, and their breakdown is exergonic. If cellular temperatures alone provided enough heat energy for these exergonic reactions to overcome their activation barriers, the essential components of a cell would disintegrate.

Note:

Art Connection
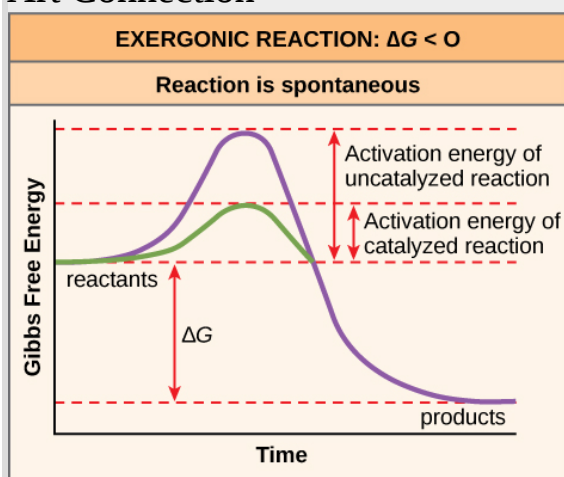
Activation energy is the energy required for a reaction to proceed, and it is lower if the reaction is catalyzed. The horizontal axis of this diagram describes the sequence of events in time.

If no activation energy were required to break down sucrose (table sugar), would you be able to store it in a sugar bowl?

Section Summary

Energy comes in many different forms. Objects in motion do physical work, and kinetic energy is the energy of objects in motion. Objects that are not in motion may have the potential to do work, and thus, have potential energy. Molecules also have potential energy because the breaking of molecular bonds has the potential to release energy. Living cells depend on the harvesting of potential energy from molecular bonds to perform work. Free energy is a measure of energy that is available to do work. The free energy of a system changes during energy transfers such as chemical reactions, and this change is referred to as ΔG.

The ΔG of a reaction can be negative or positive, meaning that the reaction releases energy or consumes energy, respectively. A reaction with a negative ΔG that gives off energy is called an exergonic reaction. One with a positive ΔG that requires energy input is called an endergonic reaction. Exergonic reactions are said to be spontaneous, because their products have less energy than their reactants. The products of endergonic reactions have a higher energy state than the reactants, and so these are nonspontaneous reactions. However, all reactions (including spontaneous -ΔG reactions) require an initial input of energy in order to reach the transition state, at which they'll proceed. This initial input of energy is called the activation energy.

Art Connections

Exercise:

  Problem:

  [link] Look at each of the processes shown, and decide if it is endergonic or exergonic. In each case, does enthalpy increase or decrease, and does entropy increase or decrease?

  Solution:

  [link] A compost pile decomposing is an exergonic process; enthalpy increases (energy is released) and entropy increases (large molecules are broken down into smaller ones). A baby developing from a fertilized egg is an endergonic process; enthalpy decreases (energy is

absorbed) and entropy decreases. Sand art being destroyed is an exergonic process; there is no change in enthalpy, but entropy increases. A ball rolling downhill is an exergonic process; enthalpy decreases (energy is released), but there is no change in entropy.

Exercise:

Problem:

[link] If no activation energy were required to break down sucrose (table sugar), would you be able to store it in a sugar bowl?

Solution:

[link] No. We can store chemical energy because of the need to overcome the barrier to its breakdown.

Review Questions

Exercise:

Problem:

Consider a pendulum swinging. Which type(s) of energy is/are associated with the pendulum in the following instances: i. the moment at which it completes one cycle, just before it begins to fall back towards the other end, ii. the moment that it is in the middle between the two ends, iii. just before it reaches the end of one cycle (just before instant i.).

   a. i. potential and kinetic, ii. potential and kinetic, iii. kinetic
   b. i. potential, ii. potential and kinetic, iii. potential and kinetic
   c. i. potential, ii. kinetic, iii. potential and kinetic
   d. i. potential and kinetic, ii. kinetic iii. kinetic

Solution:

C

Exercise:

Problem:

Which of the following comparisons or contrasts between endergonic and exergonic reactions is false?

    a. Endergonic reactions have a positive ΔG and exergonic reactions have a negative ΔG

    b. Endergonic reactions consume energy and exergonic reactions release energy

    c. Both endergonic and exergonic reactions require a small amount of energy to overcome an activation barrier

    d. Endergonic reactions take place slowly and exergonic reactions take place quickly

---

Solution:

D

Exercise:

Problem:

Which of the following is the best way to judge the relative activation energies between two given chemical reactions?

    a. Compare the ΔG values between the two reactions

    b. Compare their reaction rates

    c. Compare their ideal environmental conditions

    d. Compare the spontaneity between the two reactions

Solution:

B

Free Response

Exercise:

Problem:

Explain in your own words the difference between a spontaneous reaction and one that occurs instantaneously, and what causes this difference.

Solution:

A spontaneous reaction is one that has a negative ΔG and thus releases energy. However, a spontaneous reaction need not occur quickly or suddenly like an instantaneous reaction. It may occur over long periods due to a large energy of activation, which prevents the reaction from occurring quickly.

Exercise:

Problem:

Describe the position of the transition state on a vertical energy scale, from low to high, relative to the position of the reactants and products, for both endergonic and exergonic reactions.

Solution:

The transition state is always higher in energy than the reactants and the products of a reaction (therefore, above), regardless of whether the reaction is endergonic or exergonic.

Glossary

activation energy
    energy necessary for reactions to occur

chemical energy
    potential energy in chemical bonds that is released when those bonds are broken

endergonic
    describes chemical reactions that require energy input

enthalpy
    total energy of a system

exergonic
    describes chemical reactions that release free energy

free energy
    Gibbs free energy is the usable energy, or energy that is available to do work.

heat energy
    total bond energy of reactants or products in a chemical reaction

kinetic energy
    type of energy associated with objects or particles in motion

potential energy
    type of energy that has the potential to do work; stored energy

transition state
    high-energy, unstable state (an intermediate form between the substrate and the product) occurring during a chemical reaction

The Laws of Thermodynamics
By the end of this section, you will be able to:

- Discuss the concept of entropy
- Explain the first and second laws of thermodynamics

Thermodynamics refers to the study of energy and energy transfer involving physical matter. The matter and its environment relevant to a particular case of energy transfer are classified as a system, and everything outside of that system is called the surroundings. For instance, when heating a pot of water on the stove, the system includes the stove, the pot, and the water. Energy is transferred within the system (between the stove, pot, and water). There are two types of systems: open and closed. An open system is one in which energy can be transferred between the system and its surroundings. The stovetop system is open because heat can be lost into the air. A closed system is one that cannot transfer energy to its surroundings.

Biological organisms are open systems. Energy is exchanged between them and their surroundings, as they consume energy-storing molecules and release energy to the environment by doing work. Like all things in the physical world, energy is subject to the laws of physics. The laws of thermodynamics govern the transfer of energy in and among all systems in the universe.

The First Law of Thermodynamics

The first law of thermodynamics deals with the total amount of energy in the universe. It states that this total amount of energy is constant. In other words, there has always been, and always will be, exactly the same amount of energy in the universe. Energy exists in many different forms. According to the first law of thermodynamics, energy may be transferred from place to place or transformed into different forms, but it cannot be created or destroyed. The transfers and transformations of energy take place around us all the time. Light bulbs transform electrical energy into light energy. Gas stoves transform chemical energy from natural gas into heat energy. Plants perform one of the most biologically useful energy transformations on earth: that of converting the energy of sunlight into the chemical energy

stored within organic molecules ([link]). Some examples of energy transformations are shown in [link].

The challenge for all living organisms is to obtain energy from their surroundings in forms that they can transfer or transform into usable energy to do work. Living cells have evolved to meet this challenge very well. Chemical energy stored within organic molecules such as sugars and fats is transformed through a series of cellular chemical reactions into energy within molecules of ATP. Energy in ATP molecules is easily accessible to do work. Examples of the types of work that cells need to do include building complex molecules, transporting materials, powering the beating motion of cilia or flagella, contracting muscle fibers to create movement, and reproduction.

Energy transformations

Chemical energy

Kinetic energy

Light energy
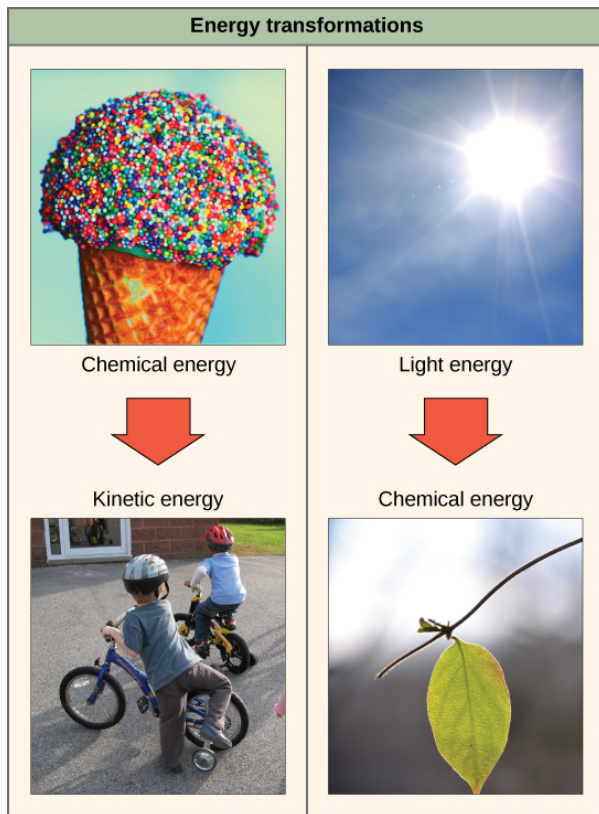
Chemical energy

Shown are two examples of energy being transferred from one system to another and

transformed from one form to another. Humans can convert the chemical energy in food, like this ice cream cone, into kinetic energy (the energy of movement to ride a bicycle). Plants can convert electromagnetic radiation (light energy) from the sun into chemical energy. (credit "ice cream": modification of work by D. Sharon Pruitt; credit "kids on bikes": modification of work by Michelle Riggen-Ransom; credit "leaf": modification of work by Cory Zanker)

The Second Law of Thermodynamics

A living cell's primary tasks of obtaining, transforming, and using energy to do work may seem simple. However, the second law of thermodynamics explains why these tasks are harder than they appear. None of the energy transfers we've discussed, along with all energy transfers and transformations in the universe, is completely efficient. In every energy transfer, some amount of energy is lost in a form that is unusable. In most cases, this form is heat energy. Thermodynamically, **heat energy** is defined as the energy transferred from one system to another that is not doing work. For example, when an airplane flies through the air, some of the energy of the flying plane is lost as heat energy due to friction with the surrounding air. This friction actually heats the air by temporarily increasing the speed of air molecules. Likewise, some energy is lost as heat energy during cellular metabolic reactions. This is good for warm-blooded creatures like us, because heat energy helps to maintain our body temperature. Strictly speaking, no energy transfer is completely efficient, because some energy is lost in an unusable form.

An important concept in physical systems is that of order and disorder (also known as randomness). The more energy that is lost by a system to its surroundings, the less ordered and more random the system is. Scientists refer to the measure of randomness or disorder within a system as **entropy**. High entropy means high disorder and low energy ([link]). To better understand entropy, think of a student's bedroom. If no energy or work were put into it, the room would quickly become messy. It would exist in a very disordered state, one of high entropy. Energy must be put into the system, in the form of the student doing work and putting everything away, in order to bring the room back to a state of cleanliness and order. This state is one of low entropy. Similarly, a car or house must be constantly maintained with work in order to keep it in an ordered state. Left alone, the entropy of the house or car gradually increases through rust and degradation. Molecules and chemical reactions have varying amounts of entropy as well. For example, as chemical reactions reach a state of equilibrium, entropy increases, and as molecules at a high concentration in one place diffuse and spread out, entropy also increases.

Note:
Scientific Connection
Transfer of Energy and the Resulting Entropy
Set up a simple experiment to understand how energy is transferred and how a change in entropy results.

1. Take a block of ice. This is water in solid form, so it has a high structural order. This means that the molecules cannot move very much and are in a fixed position. The temperature of the ice is 0°C. As a result, the entropy of the system is low.
2. Allow the ice to melt at room temperature. What is the state of molecules in the liquid water now? How did the energy transfer take place? Is the entropy of the system higher or lower? Why?
3. Heat the water to its boiling point. What happens to the entropy of the system when the water is heated?

All physical systems can be thought of in this way: Living things are highly ordered, requiring constant energy input to be maintained in a state of low entropy. As living systems take in energy-storing molecules and transform them through chemical reactions, they lose some amount of usable energy in the process, because no reaction is completely efficient. They also produce waste and by-products that aren't useful energy sources. This process increases the entropy of the system's surroundings. Since all energy transfers result in the loss of some usable energy, the second law of thermodynamics states that every energy transfer or transformation increases the entropy of the universe. Even though living things are highly ordered and maintain a state of low entropy, the entropy of the universe in total is constantly increasing due to the loss of usable energy with each energy transfer that occurs. Essentially, living things are in a continuous uphill battle against this constant increase in universal entropy.
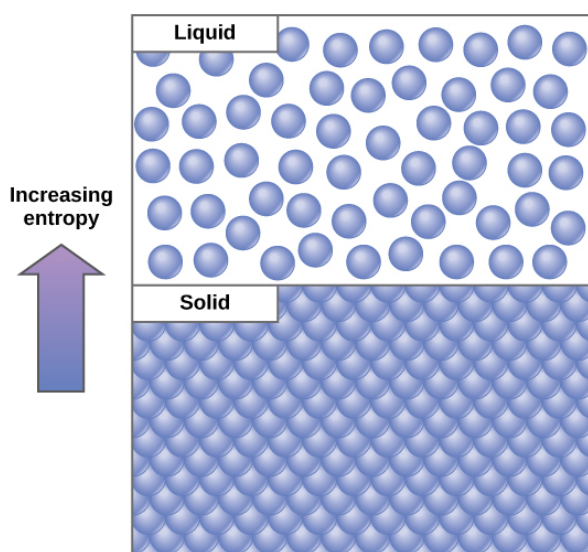
Entropy is a measure of randomness or disorder in a system. Gases have higher entropy than liquids, and liquids have higher entropy than solids.

Section Summary

In studying energy, scientists use the term "system" to refer to the matter and its environment involved in energy transfers. Everything outside of the system is called the surroundings. Single cells are biological systems. Systems can be thought of as having a certain amount of order. It takes energy to make a system more ordered. The more ordered a system is, the lower its entropy. Entropy is a measure of the disorder of a system. As a system becomes more disordered, the lower its energy and the higher its entropy become.

A series of laws, called the laws of thermodynamics, describe the properties and processes of energy transfer. The first law states that the total amount of energy in the universe is constant. This means that energy can't be created or destroyed, only transferred or transformed. The second law of thermodynamics states that every energy transfer involves some loss of energy in an unusable form, such as heat energy, resulting in a more disordered system. In other words, no energy transfer is completely efficient and tends toward disorder.

Review Questions

Exercise:

Problem:

Which of the following is not an example of an energy transformation?

    a. Turning on a light switch
    b. Solar panels at work
    c. Formation of static electricity
    d. None of the above

Solution:

A

Exercise:

Problem:

Label each of the following systems as high or low entropy: i. the instant that a perfume bottle is sprayed compared with 30 seconds later, ii. an old 1950s car compared with a brand new car, and iii. a living cell compared with a dead cell.

   a. i. low, ii. high, iii. low
   b. i. low, ii. high, iii. high
   c. i. high, ii. low, iii. high
   d. i. high, ii. low, iii. Low

Solution:

A

Free Response

Exercise:

Problem:

Imagine an elaborate ant farm with tunnels and passageways through the sand where ants live in a large community. Now imagine that an earthquake shook the ground and demolished the ant farm. In which of these two scenarios, before or after the earthquake, was the ant farm system in a state of higher or lower entropy?

Solution:

The ant farm had lower entropy before the earthquake because it was a highly ordered system. After the earthquake, the system became much more disordered and had higher entropy.

Exercise:

Problem:

Energy transfers take place constantly in everyday activities. Think of two scenarios: cooking on a stove and driving. Explain how the second law of thermodynamics applies to these two scenarios.

Solution:

While cooking, food is heating up on the stove, but not all of the heat goes to cooking the food, some of it is lost as heat energy to the surrounding air, increasing entropy. While driving, cars burn gasoline to run the engine and move the car. This reaction is not completely efficient, as some energy during this process is lost as heat energy, which is why the hood and the components underneath it heat up while the engine is turned on. The tires also heat up because of friction with the pavement, which is additional energy loss. This energy transfer, like all others, also increases entropy.

Glossary

entropy (S)
      measure of randomness or disorder within a system

heat
      energy energy transferred from one system to another that is not work (energy of the motion of molecules or particles)

thermodynamics
      study of energy and energy transfer involving physical matter

ATP: Adenosine Triphosphate
By the end of this section, you will be able to:

- Explain the role of ATP as the cellular energy currency
- Describe how energy is released through hydrolysis of ATP

Even exergonic, energy-releasing reactions require a small amount of activation energy in order to proceed. However, consider endergonic reactions, which require much more energy input, because their products have more free energy than their reactants. Within the cell, where does energy to power such reactions come from? The answer lies with an energy-supplying molecule called **adenosine triphosphate**, or **ATP**. ATP is a small, relatively simple molecule ([link]), but within some of its bonds, it contains the potential for a quick burst of energy that can be harnessed to perform cellular work. This molecule can be thought of as the primary energy currency of cells in much the same way that money is the currency that people exchange for things they need. ATP is used to power the majority of energy-requiring cellular reactions.
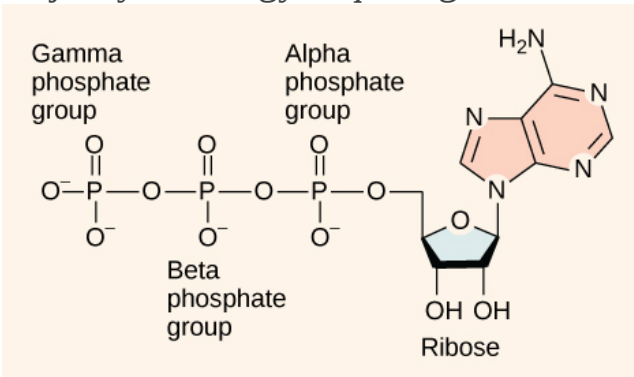
ATP is the primary energy currency of the cell. It has an adenosine backbone with three phosphate groups attached.

As its name suggests, adenosine triphosphate is comprised of adenosine bound to three phosphate groups ([link]). Adenosine is a nucleoside consisting of the nitrogenous base adenine and a five-carbon sugar, ribose.

The three phosphate groups, in order of closest to furthest from the ribose sugar, are labeled alpha, beta, and gamma. Together, these chemical groups constitute an energy powerhouse. However, not all bonds within this molecule exist in a particularly high-energy state. Both bonds that link the phosphates are equally high-energy bonds (**phosphoanhydride bonds**) that, when broken, release sufficient energy to power a variety of cellular reactions and processes. These high-energy bonds are the bonds between the second and third (or beta and gamma) phosphate groups and between the first and second phosphate groups. The reason that these bonds are considered "high-energy" is because the products of such bond breaking— adenosine diphosphate (ADP) and one inorganic phosphate group (P_i)— have considerably lower free energy than the reactants: ATP and a water molecule. Because this reaction takes place with the use of a water molecule, it is considered a hydrolysis reaction. In other words, ATP is hydrolyzed into ADP in the following reaction:
Equation:

$$ATP + H_2O \rightarrow ADP + P_i + \text{free energy}$$

Like most chemical reactions, the hydrolysis of ATP to ADP is reversible. The reverse reaction regenerates ATP from ADP + P_i. Indeed, cells rely on the regeneration of ATP just as people rely on the regeneration of spent money through some sort of income. Since ATP hydrolysis releases energy, ATP regeneration must require an input of free energy. The formation of ATP is expressed in this equation:
Equation:

$$ADP + P_i + \text{free energy} \rightarrow ATP + H_2O$$

Two prominent questions remain with regard to the use of ATP as an energy source. Exactly how much free energy is released with the hydrolysis of ATP, and how is that free energy used to do cellular work? The calculated ΔG for the hydrolysis of one mole of ATP into ADP and P_i is −7.3 kcal/mole (−30.5 kJ/mol). Since this calculation is true under standard conditions, it would be expected that a different value exists under cellular conditions. In fact, the ΔG for the hydrolysis of one mole of ATP in a living

cell is almost double the value at standard conditions: −14 kcal/mol (−57 kJ/mol).

ATP is a highly unstable molecule. Unless quickly used to perform work, ATP spontaneously dissociates into ADP + P_i, and the free energy released during this process is lost as heat. The second question posed above, that is, how the energy released by ATP hydrolysis is used to perform work inside the cell, depends on a strategy called energy coupling. Cells couple the exergonic reaction of ATP hydrolysis with endergonic reactions, allowing them to proceed. One example of energy coupling using ATP involves a transmembrane ion pump that is extremely important for cellular function. This sodium-potassium pump (Na^+/K^+ pump) drives sodium out of the cell and potassium into the cell ([link]). A large percentage of a cell's ATP is spent powering this pump, because cellular processes bring a great deal of sodium into the cell and potassium out of the cell. The pump works constantly to stabilize cellular concentrations of sodium and potassium. In order for the pump to turn one cycle (exporting three Na+ ions and importing two K^+ ions), one molecule of ATP must be hydrolyzed. When ATP is hydrolyzed, its gamma phosphate doesn't simply float away, but is actually transferred onto the pump protein. This process of a phosphate group binding to a molecule is called phosphorylation. As with most cases of ATP hydrolysis, a phosphate from ATP is transferred onto another molecule. In a phosphorylated state, the Na^+/K^+ pump has more free energy and is triggered to undergo a conformational change. This change allows it to release Na^+ to the outside of the cell. It then binds extracellular K^+, which, through another conformational change, causes the phosphate to detach from the pump. This release of phosphate triggers the K^+ to be released to the inside of the cell. Essentially, the energy released from the hydrolysis of ATP is coupled with the energy required to power the pump and transport Na^+ and K^+ ions. ATP performs cellular work using this basic form of energy coupling through phosphorylation.

Note:
Art Connection

Sodium-Potassium Pump
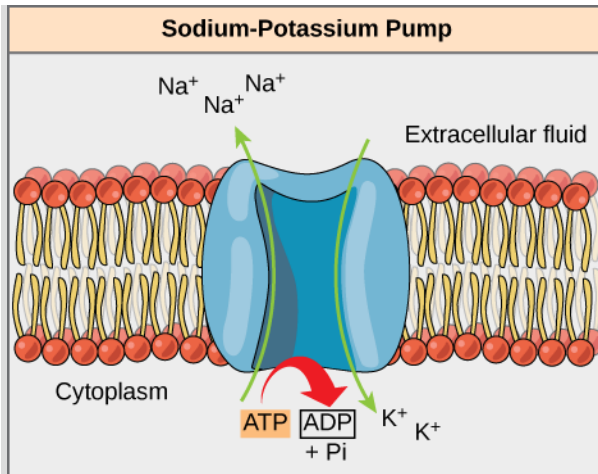
The sodium-potassium pump is an example of energy coupling. The energy derived from exergonic ATP hydrolysis is used to pump sodium and potassium ions across the cell membrane.

The hydrolysis of one ATP molecule releases 7.3 kcal/mol of energy ($\Delta G = -7.3$ kcal/mol of energy). If it takes 2.1 kcal/mol of energy to move one Na^+ across the membrane ($\Delta G = +2.1$ kcal/mol of energy), how many sodium ions could be moved by the hydrolysis of one ATP molecule?

Often during cellular metabolic reactions, such as the synthesis and breakdown of nutrients, certain molecules must be altered slightly in their conformation to become substrates for the next step in the reaction series. One example is during the very first steps of cellular respiration, when a molecule of the sugar glucose is broken down in the process of glycolysis. In the first step of this process, ATP is required for the phosphorylation of glucose, creating a high-energy but unstable intermediate. This phosphorylation reaction powers a conformational change that allows the phosphorylated glucose molecule to be converted to the phosphorylated sugar fructose. Fructose is a necessary intermediate for glycolysis to move

forward. Here, the exergonic reaction of ATP hydrolysis is coupled with the endergonic reaction of converting glucose into a phosphorylated intermediate in the pathway. Once again, the energy released by breaking a phosphate bond within ATP was used for the phosphorylation of another molecule, creating an unstable intermediate and powering an important conformational change.

Section Summary

ATP is the primary energy-supplying molecule for living cells. ATP is made up of a nucleotide, a five-carbon sugar, and three phosphate groups. The bonds that connect the phosphates (phosphoanhydride bonds) have high-energy content. The energy released from the hydrolysis of ATP into ADP + P_i is used to perform cellular work. Cells use ATP to perform work by coupling the exergonic reaction of ATP hydrolysis with endergonic reactions. ATP donates its phosphate group to another molecule via a process known as phosphorylation. The phosphorylated molecule is at a higher-energy state and is less stable than its unphosphorylated form, and this added energy from the addition of the phosphate allows the molecule to undergo its endergonic reaction.

Art Connections

Exercise:

Problem:

[link] The hydrolysis of one ATP molecule releases 7.3 kcal/mol of energy (ΔG = −7.3 kcal/mol of energy). If it takes 2.1 kcal/mol of energy to move one Na^+ across the membrane (ΔG = +2.1 kcal/mol of energy), how many sodium ions could be moved by the hydrolysis of one ATP molecule?

Solution:

[link] Three sodium ions could be moved by the hydrolysis of one ATP molecule. The ΔG of the coupled reaction must be negative. Movement of three sodium ions across the membrane will take 6.3 kcal of energy (2.1 kcal × 3 Na^+ ions = 6.3 kcal). Hydrolysis of ATP provides 7.3 kcal of energy, more than enough to power this reaction. Movement of four sodium ions across the membrane, however, would require 8.4 kcal of energy, more than one ATP molecule can provide.

Review Questions

Exercise:

Problem: The energy released by the hydrolysis of ATP is

    a. primarily stored between the alpha and beta phosphates
    b. equal to −57 kcal/mol
    c. harnessed as heat energy by the cell to perform work
    d. providing energy to coupled reactions

Solution:

D

Exercise:

Problem:

Which of the following molecules is likely to have the most potential energy?

    a. sucrose
    b. ATP
    c. glucose
    d. ADP

Solution:

A

Free Response

Exercise:

Problem:

Do you think that the E_A for ATP hydrolysis is relatively low or high? Explain your reasoning.

Solution:

The activation energy for hydrolysis is very low. Not only is ATP hydrolysis an exergonic process with a large $-\Delta G$, but ATP is also a very unstable molecule that rapidly breaks down into ADP + P_i if not utilized quickly. This suggests a very low E_A since it hydrolyzes so quickly.

Glossary

ATP

adenosine triphosphate, the cell's energy currency

phosphoanhydride bond
    bond that connects phosphates in an ATP molecule

Enzymes
By the end of this section, you will be able to:

- Describe the role of enzymes in metabolic pathways
- Explain how enzymes function as molecular catalysts
- Discuss enzyme regulation by various factors

A substance that helps a chemical reaction to occur is a catalyst, and the special molecules that catalyze biochemical reactions are called enzymes. Almost all enzymes are proteins, made up of chains of amino acids, and they perform the critical task of lowering the activation energies of chemical reactions inside the cell. Enzymes do this by binding to the reactant molecules, and holding them in such a way as to make the chemical bond-breaking and bond-forming processes take place more readily. It is important to remember that enzymes don't change the ΔG of a reaction. In other words, they don't change whether a reaction is exergonic (spontaneous) or endergonic. This is because they don't change the free energy of the reactants or products. They only reduce the activation energy required to reach the transition state ([link]).
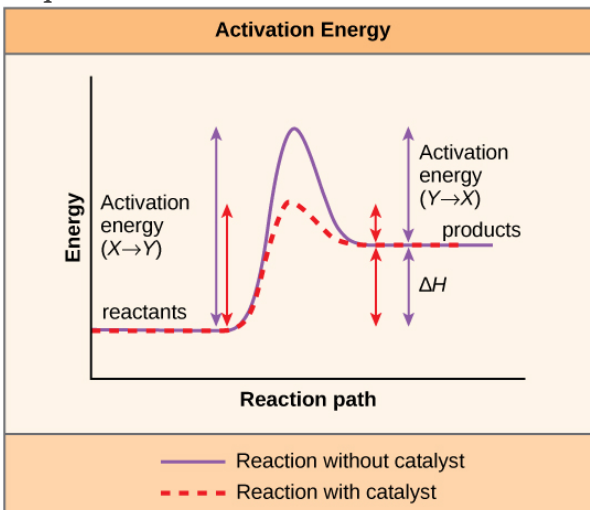
Enzymes lower the activation energy of the reaction but do not change the free energy of the reaction.

Enzyme Active Site and Substrate Specificity

The chemical reactants to which an enzyme binds are the enzyme's **substrates**. There may be one or more substrates, depending on the particular chemical reaction. In some reactions, a single-reactant substrate is broken down into multiple products. In others, two substrates may come together to create one larger molecule. Two reactants might also enter a reaction, both become modified, and leave the reaction as two products. The location within the enzyme where the substrate binds is called the enzyme's **active site**. The active site is where the "action" happens, so to speak. Since enzymes are proteins, there is a unique combination of amino acid residues (also called side chains, or R groups) within the active site. Each residue is characterized by different properties. Residues can be large or small, weakly acidic or basic, hydrophilic or hydrophobic, positively or negatively charged, or neutral. The unique combination of amino acid residues, their positions, sequences, structures, and properties, creates a very specific chemical environment within the active site. This specific environment is suited to bind, albeit briefly, to a specific chemical substrate (or substrates). Due to this jigsaw puzzle-like match between an enzyme and its substrates (which adapts to find the best fit between the transition state and the active site), enzymes are known for their specificity. The "best fit" results from the shape and the amino acid functional group's attraction to the substrate. There is a specifically matched enzyme for each substrate and, thus, for each chemical reaction; however, there is flexibility as well.

The fact that active sites are so perfectly suited to provide specific environmental conditions also means that they are subject to influences by the local environment. It is true that increasing the environmental temperature generally increases reaction rates, enzyme-catalyzed or otherwise. However, increasing or decreasing the temperature outside of an optimal range can affect chemical bonds within the active site in such a way that they are less well suited to bind substrates. High temperatures will eventually cause enzymes, like other biological molecules, to **denature**, a process that changes the natural properties of a substance. Likewise, the pH of the local environment can also affect enzyme function. Active site amino acid residues have their own acidic or basic properties that are optimal for catalysis. These residues are sensitive to changes in pH that can impair the

way substrate molecules bind. Enzymes are suited to function best within a certain pH range, and, as with temperature, extreme pH values (acidic or basic) of the environment can cause enzymes to denature.

Induced Fit and Enzyme Function

For many years, scientists thought that enzyme-substrate binding took place in a simple "lock-and-key" fashion. This model asserted that the enzyme and substrate fit together perfectly in one instantaneous step. However, current research supports a more refined view called **induced fit** ([link]). The induced-fit model expands upon the lock-and-key model by describing a more dynamic interaction between enzyme and substrate. As the enzyme and substrate come together, their interaction causes a mild shift in the enzyme's structure that confirms an ideal binding arrangement between the enzyme and the transition state of the substrate. This ideal binding maximizes the enzyme's ability to catalyze its reaction.

When an enzyme binds its substrate, an enzyme-substrate complex is formed. This complex lowers the activation energy of the reaction and promotes its rapid progression in one of many ways. On a basic level, enzymes promote chemical reactions that involve more than one substrate

by bringing the substrates together in an optimal orientation. The appropriate region (atoms and bonds) of one molecule is juxtaposed to the appropriate region of the other molecule with which it must react. Another way in which enzymes promote the reaction of their substrates is by creating an optimal environment within the active site for the reaction to occur. Certain chemical reactions might proceed best in a slightly acidic or non-polar environment. The chemical properties that emerge from the particular arrangement of amino acid residues within an active site create the perfect environment for an enzyme's specific substrates to react.

You've learned that the activation energy required for many reactions includes the energy involved in manipulating or slightly contorting chemical bonds so that they can easily break and allow others to reform. Enzymatic action can aid this process. The enzyme-substrate complex can lower the activation energy by contorting substrate molecules in such a way as to facilitate bond-breaking, helping to reach the transition state. Finally, enzymes can also lower activation energies by taking part in the chemical reaction itself. The amino acid residues can provide certain ions or chemical groups that actually form covalent bonds with substrate molecules as a necessary step of the reaction process. In these cases, it is important to remember that the enzyme will always return to its original state at the completion of the reaction. One of the hallmark properties of enzymes is that they remain ultimately unchanged by the reactions they catalyze. After an enzyme is done catalyzing a reaction, it releases its product(s).
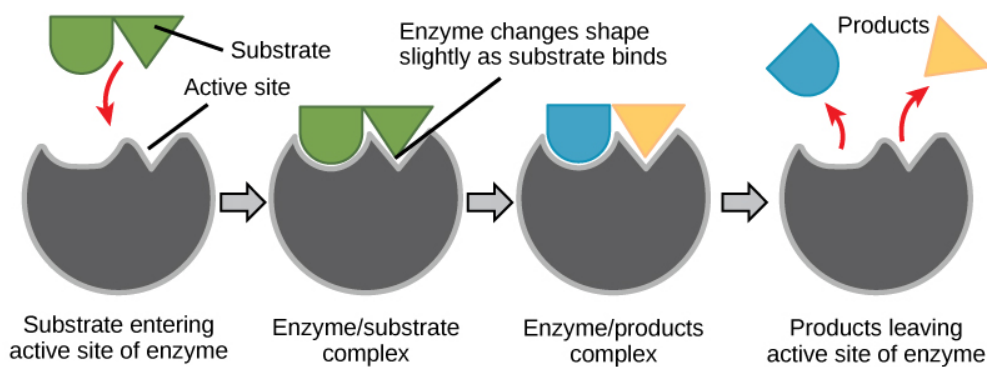
According to the induced-fit model, both enzyme and

substrate undergo dynamic conformational changes upon binding. The enzyme contorts the substrate into its transition state, thereby increasing the rate of the reaction.

Control of Metabolism Through Enzyme Regulation

It would seem ideal to have a scenario in which all of the enzymes encoded in an organism's genome existed in abundant supply and functioned optimally under all cellular conditions, in all cells, at all times. In reality, this is far from the case. A variety of mechanisms ensure that this does not happen. Cellular needs and conditions vary from cell to cell, and change within individual cells over time. The required enzymes and energetic demands of stomach cells are different from those of fat storage cells, skin cells, blood cells, and nerve cells. Furthermore, a digestive cell works much harder to process and break down nutrients during the time that closely follows a meal compared with many hours after a meal. As these cellular demands and conditions vary, so do the amounts and functionality of different enzymes.

Since the rates of biochemical reactions are controlled by activation energy, and enzymes lower and determine activation energies for chemical reactions, the relative amounts and functioning of the variety of enzymes within a cell ultimately determine which reactions will proceed and at which rates. This determination is tightly controlled. In certain cellular environments, enzyme activity is partly controlled by environmental factors, like pH and temperature. There are other mechanisms through which cells control the activity of enzymes and determine the rates at which various biochemical reactions will occur.

Regulation of Enzymes by Molecules

Enzymes can be regulated in ways that either promote or reduce their activity. There are many different kinds of molecules that inhibit or promote enzyme function, and various mechanisms exist for doing so. In some cases of enzyme inhibition, for example, an inhibitor molecule is similar enough to a substrate that it can bind to the active site and simply block the substrate from binding. When this happens, the enzyme is inhibited through **competitive inhibition**, because an inhibitor molecule competes with the substrate for active site binding ([link]). On the other hand, in noncompetitive inhibition, an inhibitor molecule binds to the enzyme in a location other than an allosteric site and still manages to block substrate binding to the active site.
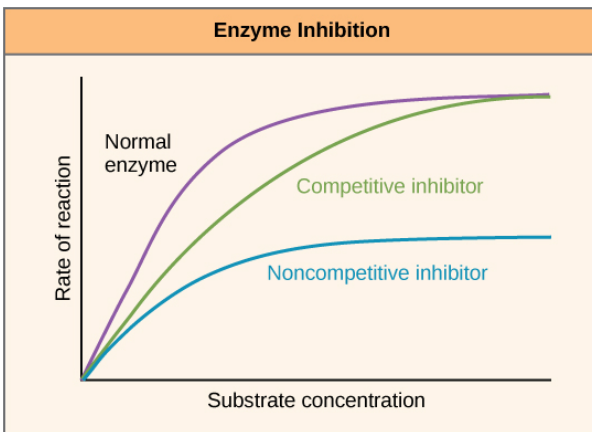

Competitive and noncompetitive inhibition affect the rate of reaction differently. Competitive inhibitors affect the initial rate but do not affect the maximal rate, whereas noncompetitive inhibitors affect the maximal rate.

Some inhibitor molecules bind to enzymes in a location where their binding induces a conformational change that reduces the affinity of the enzyme for

its substrate. This type of inhibition is called **allosteric inhibition** ([link]). Most allosterically regulated enzymes are made up of more than one polypeptide, meaning that they have more than one protein subunit. When an allosteric inhibitor binds to an enzyme, all active sites on the protein subunits are changed slightly such that they bind their substrates with less efficiency. There are allosteric activators as well as inhibitors. Allosteric activators bind to locations on an enzyme away from the active site, inducing a conformational change that increases the affinity of the enzyme's active site(s) for its substrate(s).
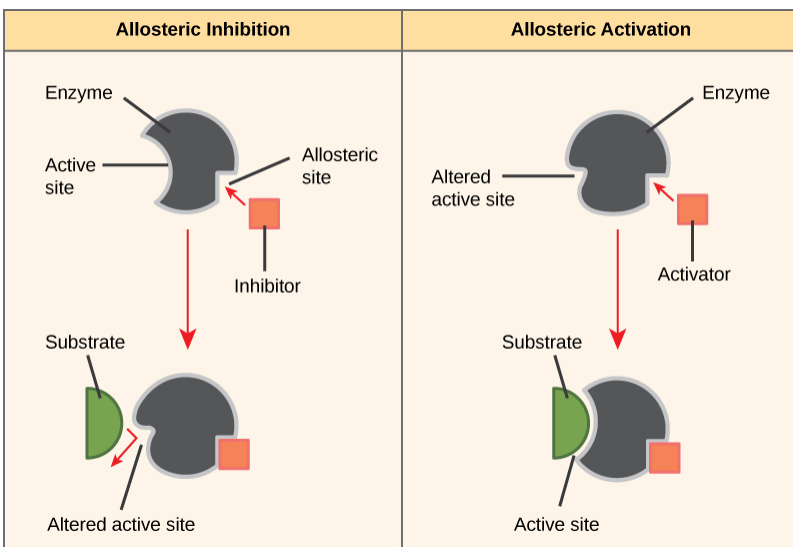
Allosteric inhibitors modify the active site of the enzyme so that substrate binding is reduced or prevented. In contrast, allosteric activators modify the active site of the enzyme so that the affinity for the substrate increases.

Note:
Everyday Connection

Have you ever wondered how pharmaceutical drugs are developed? (credit: Deborah Austin)

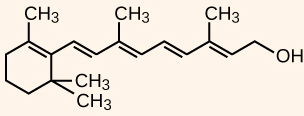**Drug Discovery by Looking for Inhibitors of Key Enzymes in Specific Pathways**
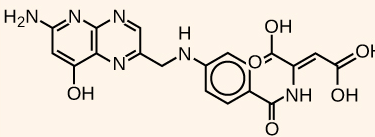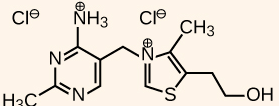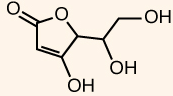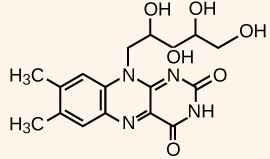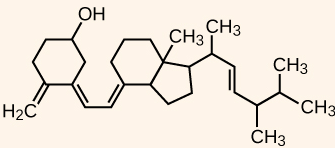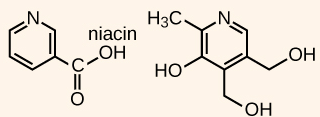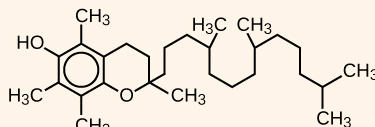
Enzymes are key components of metabolic pathways. Understanding how enzymes work and how they can be regulated is a key principle behind the development of many of the pharmaceutical drugs ([link]) on the market today. Biologists working in this field collaborate with other scientists, usually chemists, to design drugs.

Consider statins for example—which is the name given to the class of drugs that reduces cholesterol levels. These compounds are essentially inhibitors of the enzyme HMG-CoA reductase. HMG-CoA reductase is the enzyme that synthesizes cholesterol from lipids in the body. By inhibiting this enzyme, the levels of cholesterol synthesized in the body can be reduced. Similarly, acetaminophen, popularly marketed under the brand name Tylenol, is an inhibitor of the enzyme cyclooxygenase. While it is effective in providing relief from fever and inflammation (pain), its mechanism of action is still not completely understood.

How are drugs developed? One of the first challenges in drug development is identifying the specific molecule that the drug is intended to target. In the case of statins, HMG-CoA reductase is the drug target. Drug targets are identified through painstaking research in the laboratory. Identifying the

target alone is not sufficient; scientists also need to know how the target acts inside the cell and which reactions go awry in the case of disease. Once the target and the pathway are identified, then the actual process of drug design begins. During this stage, chemists and biologists work together to design and synthesize molecules that can either block or activate a particular reaction. However, this is only the beginning: both if and when a drug prototype is successful in performing its function, then it must undergo many tests from in vitro experiments to clinical trials before it can get FDA approval to be on the market.

Many enzymes don't work optimally, or even at all, unless bound to other specific non-protein helper molecules, either temporarily through ionic or hydrogen bonds or permanently through stronger covalent bonds. Two types of helper molecules are **cofactors** and **coenzymes**. Binding to these molecules promotes optimal conformation and function for their respective enzymes. Cofactors are inorganic ions such as iron (Fe++) and magnesium (Mg++). One example of an enzyme that requires a metal ion as a cofactor is the enzyme that builds DNA molecules, DNA polymerase, which requires bound zinc ion (Zn++) to function. Coenzymes are organic helper molecules, with a basic atomic structure made up of carbon and hydrogen, which are required for enzyme action. The most common sources of coenzymes are dietary vitamins ([link]). Some vitamins are precursors to coenzymes and others act directly as coenzymes. Vitamin C is a coenzyme for multiple enzymes that take part in building the important connective tissue component, collagen. An important step in the breakdown of glucose to yield energy is catalysis by a multi-enzyme complex called pyruvate dehydrogenase. Pyruvate dehydrogenase is a complex of several enzymes that actually requires one cofactor (a magnesium ion) and five different organic coenzymes to catalyze its specific chemical reaction. Therefore, enzyme function is, in part, regulated by an abundance of various cofactors and coenzymes, which are supplied primarily by the diets of most organisms.

Dietary Vitamins	
Vitamin A	**Folic acid**
Vitamin B$_1$	**Vitamin C**
Vitamin B$_2$	**Vitamin D$_2$ (calciferol)**
Vitamin B$_6$ (pyridoxine)	**Vitamin E (*alpha*-tocopherol)**

Vitamins are important coenzymes or precursors of coenzymes, and are required for enzymes to function properly. Multivitamin capsules usually contain mixtures of all the vitamins at different percentages.

Enzyme Compartmentalization

In eukaryotic cells, molecules such as enzymes are usually compartmentalized into different organelles. This allows for yet another level of regulation of enzyme activity. Enzymes required only for certain cellular processes can be housed separately along with their substrates, allowing for more efficient chemical reactions. Examples of this sort of

enzyme regulation based on location and proximity include the enzymes involved in the latter stages of cellular respiration, which take place exclusively in the mitochondria, and the enzymes involved in the digestion of cellular debris and foreign materials, located within lysosomes.

Feedback Inhibition in Metabolic Pathways

Molecules can regulate enzyme function in many ways. A major question remains, however: What are these molecules and where do they come from? Some are cofactors and coenzymes, ions, and organic molecules, as you've learned. What other molecules in the cell provide enzymatic regulation, such as allosteric modulation, and competitive and noncompetitive inhibition? The answer is that a wide variety of molecules can perform these roles. Some of these molecules include pharmaceutical and non-pharmaceutical drugs, toxins, and poisons from the environment. Perhaps the most relevant sources of enzyme regulatory molecules, with respect to cellular metabolism, are the products of the cellular metabolic reactions themselves. In a most efficient and elegant way, cells have evolved to use the products of their own reactions for feedback inhibition of enzyme activity. **Feedback inhibition** involves the use of a reaction product to regulate its own further production ([link]). The cell responds to the abundance of specific products by slowing down production during anabolic or catabolic reactions. Such reaction products may inhibit the enzymes that catalyzed their production through the mechanisms described above.
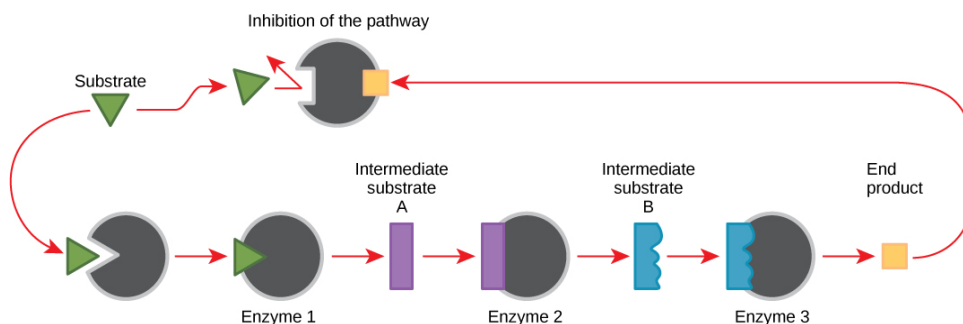
Metabolic pathways are a series of reactions catalyzed by multiple enzymes. Feedback inhibition, where the end product of the pathway inhibits an upstream step, is an important regulatory mechanism in cells.

The production of both amino acids and nucleotides is controlled through feedback inhibition. Additionally, ATP is an allosteric regulator of some of the enzymes involved in the catabolic breakdown of sugar, the process that produces ATP. In this way, when ATP is abundant, the cell can prevent its further production. Remember that ATP is an unstable molecule that can spontaneously dissociate into ADP. If too much ATP were present in a cell, much of it would go to waste. On the other hand, ADP serves as a positive allosteric regulator (an allosteric activator) for some of the same enzymes that are inhibited by ATP. Thus, when relative levels of ADP are high compared to ATP, the cell is triggered to produce more ATP through the catabolism of sugar.

Section Summary

Enzymes are chemical catalysts that accelerate chemical reactions at physiological temperatures by lowering their activation energy. Enzymes are usually proteins consisting of one or more polypeptide chains. Enzymes have an active site that provides a unique chemical environment, made up of certain amino acid R groups (residues). This unique environment is perfectly suited to convert particular chemical reactants for that enzyme, called substrates, into unstable intermediates called transition states. Enzymes and substrates are thought to bind with an induced fit, which means that enzymes undergo slight conformational adjustments upon substrate contact, leading to full, optimal binding. Enzymes bind to substrates and catalyze reactions in four different ways: bringing substrates together in an optimal orientation, compromising the bond structures of substrates so that bonds can be more easily broken, providing optimal environmental conditions for a reaction to occur, or participating directly in their chemical reaction by forming transient covalent bonds with the substrates.

Enzyme action must be regulated so that in a given cell at a given time, the desired reactions are being catalyzed and the undesired reactions are not. Enzymes are regulated by cellular conditions, such as temperature and pH. They are also regulated through their location within a cell, sometimes being compartmentalized so that they can only catalyze reactions under certain circumstances. Inhibition and activation of enzymes via other molecules are other important ways that enzymes are regulated. Inhibitors can act competitively, noncompetitively, or allosterically; noncompetitive inhibitors are usually allosteric. Activators can also enhance the function of enzymes allosterically. The most common method by which cells regulate the enzymes in metabolic pathways is through feedback inhibition. During feedback inhibition, the products of a metabolic pathway serve as inhibitors (usually allosteric) of one or more of the enzymes (usually the first committed enzyme of the pathway) involved in the pathway that produces them.

Review Questions

Exercise:

Problem: Which of the following is not true about enzymes:

    a. They increase ΔG of reactions
    b. They are usually made of amino acids
    c. They lower the activation energy of chemical reactions
    d. Each one is specific to the particular substrate(s) to which it binds

Solution:

A

Exercise:

Problem: An allosteric inhibitor does which of the following?

a. Binds to an enzyme away from the active site and changes the conformation of the active site, increasing its affinity for substrate binding
b. Binds to the active site and blocks it from binding substrate
c. Binds to an enzyme away from the active site and changes the conformation of the active site, decreasing its affinity for the substrate
d. Binds directly to the active site and mimics the substrate

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Solution:

C

Exercise:

Problem:

Which of the following analogies best describe the induced-fit model of enzyme-substrate binding?

a. A hug between two people
b. A key fitting into a lock
c. A square peg fitting through the square hole and a round peg fitting through the round hole of a children's toy
d. The fitting together of two jigsaw puzzle pieces.

Solution:

A

Free Response

Exercise:

Problem:

With regard to enzymes, why are vitamins necessary for good health? Give examples.

Solution:

Most vitamins and minerals act as coenzymes and cofactors for enzyme action. Many enzymes require the binding of certain cofactors or coenzymes to be able to catalyze their reactions. Since enzymes catalyze many important reactions, it is critical to obtain sufficient vitamins and minerals from the diet and from supplements. Vitamin C (ascorbic acid) is a coenzyme necessary for the action of enzymes that build collagen, an important protein component of connective tissue throughout the body. Magnesium ion (Mg^{++}) is an important cofactor that is necessary for the enzyme pyruvate dehydrogenase to catalyze part of the pathway that breaks down sugar to produce energy. Vitamins cannot be produced in the human body and therefore must be obtained in the diet.

Exercise:

Problem:

Explain in your own words how enzyme feedback inhibition benefits a cell.

Solution:

Feedback inhibition allows cells to control the amounts of metabolic products produced. If there is too much of a particular product relative to what the cell's needs, feedback inhibition effectively causes the cell to decrease production of that particular product. In general, this reduces the production of superfluous products and conserves energy, maximizing energy efficiency.

Glossary

active site
    specific region of the enzyme to which the substrate binds

allosteric inhibition
    inhibition by a binding event at a site different from the active site,
    which induces a conformational change and reduces the affinity of the
    enzyme for its substrate

coenzyme
    small organic molecule, such as a vitamin or its derivative, which is
    required to enhance the activity of an enzyme

cofactor
    inorganic ion, such as iron and magnesium ions, required for optimal
    regulation of enzyme activity

competitive inhibition
    type of inhibition in which the inhibitor competes with the substrate
    molecule by binding to the active site of the enzyme

denature
    process that changes the natural properties of a substance

feedback inhibition
    effect of a product of a reaction sequence to decrease its further
    production by inhibiting the activity of the first enzyme in the pathway
    that produces it

induced fit
    dynamic fit between the enzyme and its substrate, in which both
    components modify their structures to allow for ideal binding

substrate
    molecule on which the enzyme acts

Introduction
class="introduction"

This geothermal energy plant transforms thermal energy from deep in the ground into electrical energy, which can be easily used. (credit: modification of work by the U.S. Department of Defense)

The electrical energy plant in [link] converts energy from one form to another form that can be more easily used. This type of generating plant starts with underground thermal energy (heat) and transforms it into electrical energy that will be transported to homes and factories. Like a generating plant, plants and animals also must take in energy from the environment and convert it into a form that their cells can use. Energy enters an organism's body in one form and is converted into another form that can fuel the organism's life functions. In the process of photosynthesis, plants and other photosynthetic producers take in energy in the form of light (solar energy) and convert it into chemical energy, glucose, which stores this energy in its chemical bonds. Then, a series of metabolic pathways, collectively called cellular respiration, extracts the energy from the bonds in glucose and converts it into a form that all living things can use—both producers, such as plants, and consumers, such as animals.

Energy in Living Systems
By the end of this section, you will be able to:

- Discuss the importance of electrons in the transfer of energy in living systems
- Explain how ATP is used by the cell as an energy source

Energy production within a cell involves many coordinated chemical pathways. Most of these pathways are combinations of oxidation and reduction reactions. Oxidation and reduction occur in tandem. An oxidation reaction strips an electron from an atom in a compound, and the addition of this electron to another compound is a reduction reaction. Because oxidation and reduction usually occur together, these pairs of reactions are called oxidation reduction reactions, or **redox reactions**.
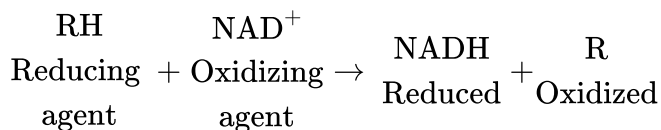
Electrons and Energy

The removal of an electron from a molecule, oxidizing it, results in a decrease in potential energy in the oxidized compound. The electron (sometimes as part of a hydrogen atom), does not remain unbonded, however, in the cytoplasm of a cell. Rather, the electron is shifted to a second compound, reducing the second compound. The shift of an electron from one compound to another removes some potential energy from the first compound (the oxidized compound) and increases the potential energy of the second compound (the reduced compound). The transfer of electrons between molecules is important because most of the energy stored in atoms and used to fuel cell functions is in the form of high-energy electrons. The transfer of energy in the form of electrons allows the cell to transfer and use energy in an incremental fashion—in small packages rather than in a single, destructive burst. This chapter focuses on the extraction of energy from food; you will see that as you track the path of the transfers, you are tracking the path of electrons moving through metabolic pathways.

Electron Carriers

In living systems, a small class of compounds functions as electron shuttles: They bind and carry high-energy electrons between compounds in pathways. The principal electron carriers we will consider are derived from the B vitamin group and are derivatives of nucleotides. These compounds can be easily reduced (that is, they accept electrons) or oxidized (they lose electrons). Nicotinamide adenine dinucleotide (NAD) ([link]) is derived from vitamin B3, niacin. NAD^+ is the oxidized form of the molecule; NADH is the reduced form of the molecule after it has accepted two electrons and a proton (which together are the equivalent of a hydrogen atom with an extra electron).

NAD^+ can accept electrons from an organic molecule according to the general equation:
Equation:

$$\underset{\substack{\text{Reducing} \\ \text{agent}}}{RH} + \underset{\substack{\text{Oxidizing} \\ \text{agent}}}{NAD^+} \rightarrow \underset{\text{Reduced}}{NADH} + \underset{\text{Oxidized}}{R}$$

When electrons are added to a compound, they are reduced. A compound that reduces another is called a reducing agent. In the above equation, RH is a reducing agent, and NAD^+ is reduced to NADH. When electrons are removed from compound, it oxidized. A compound that oxidizes another is called an oxidizing agent. In the above equation, NAD^+ is an oxidizing agent, and RH is oxidized to R.

Similarly, flavin adenine dinucleotide (FAD^+) is derived from vitamin B_2, also called riboflavin. Its reduced form is $FADH_2$. A second variation of NAD, NADP, contains an extra phosphate group. Both NAD^+ and FAD^+ are extensively used in energy extraction from sugars, and NADP plays an important role in anabolic reactions and photosynthesis.
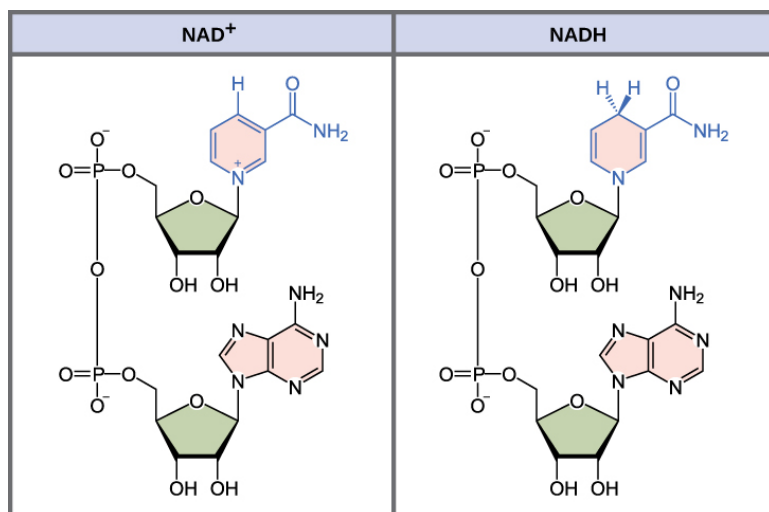
The oxidized form of the electron carrier (NAD^+) is shown on the left and the reduced form (NADH) is shown on the right. The nitrogenous base in NADH has one more hydrogen ion and two more electrons than in NAD^+.

ATP in Living Systems

A living cell cannot store significant amounts of free energy. Excess free energy would result in an increase of heat in the cell, which would result in excessive thermal motion that could damage and then destroy the cell. Rather, a cell must be able to handle that energy in a way that enables the cell to store energy safely and release it for use only as needed. Living cells accomplish this by using the compound adenosine triphosphate (ATP). ATP is often called the "energy currency" of the cell, and, like currency, this versatile compound can be used to fill any energy need of the cell. How? It functions similarly to a rechargeable battery.

When ATP is broken down, usually by the removal of its terminal phosphate group, energy is released. The energy is used to do work by the cell, usually by the released phosphate binding to

another molecule, activating it. For example, in the mechanical work of muscle contraction, ATP supplies the energy to move the contractile muscle proteins. Recall the active transport work of the sodium-potassium pump in cell membranes. ATP alters the structure of the integral protein that functions as the pump, changing its affinity for sodium and potassium. In this way, the cell performs work, pumping ions against their electrochemical gradients.

ATP Structure and Function

At the heart of ATP is a molecule of adenosine monophosphate (AMP), which is composed of an adenine molecule bonded to a ribose molecule and to a single phosphate group ([link]). Ribose is a five-carbon sugar found in RNA, and AMP is one of the nucleotides in RNA. The addition of a second phosphate group to this core molecule results in the formation of adenosine diphosphate (ADP); the addition of a third phosphate group forms adenosine triphosphate (ATP).
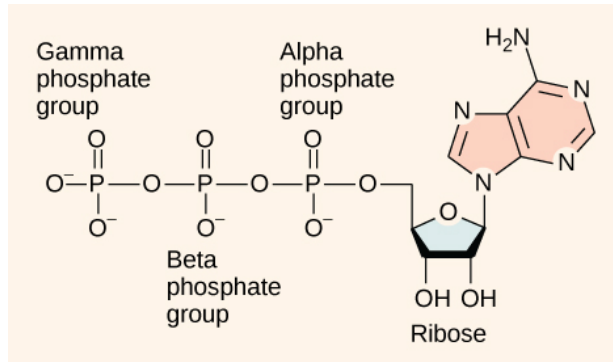
ATP (adenosine triphosphate) has three phosphate groups that can be removed by hydrolysis to form ADP (adenosine diphosphate) or AMP (adenosine monophosphate).The negative charges on the phosphate group naturally repel each other, requiring energy to bond them together and releasing energy when these bonds are broken.

The addition of a phosphate group to a molecule requires energy. Phosphate groups are negatively charged and thus repel one another when they are arranged in series, as they are in ADP and ATP. This repulsion makes the ADP and ATP molecules inherently unstable. The release of one or two phosphate groups from ATP, a process called **dephosphorylation**, releases energy.

Energy from ATP

Hydrolysis is the process of breaking complex macromolecules apart. During hydrolysis, water is split, or lysed, and the resulting hydrogen atom (H^+) and a hydroxyl group (OH^-) are added to the larger molecule. The hydrolysis of ATP produces ADP, together with an inorganic phosphate ion (P_i), and the release of free energy. To carry out life processes, ATP is continuously broken down into ADP, and like a rechargeable battery, ADP is continuously regenerated into ATP by the reattachment of a third phosphate group. Water, which was broken down into its hydrogen atom and hydroxyl group during ATP hydrolysis, is regenerated when a third phosphate is added to the ADP molecule, reforming ATP.

Obviously, energy must be infused into the system to regenerate ATP. Where does this energy come from? In nearly every living thing on earth, the energy comes from the metabolism of glucose. In this way, ATP is a direct link between the limited set of exergonic pathways of glucose catabolism and the multitude of endergonic pathways that power living cells.

Phosphorylation

Recall that, in some chemical reactions, enzymes may bind to several substrates that react with each other on the enzyme, forming an intermediate complex. An intermediate complex is a temporary structure, and it allows one of the substrates (such as ATP) and reactants to more readily react with each other; in reactions involving ATP, ATP is one of the substrates and ADP is a product. During an endergonic chemical reaction, ATP forms an intermediate complex with the substrate and enzyme in the reaction. This intermediate complex allows the ATP to transfer its third phosphate group, with its energy, to the substrate, a process called phosphorylation. **Phosphorylation** refers to the addition of the phosphate (~P). This is illustrated by the following generic reaction:
Equation:

$$A + enzyme + ATP \rightarrow \ [A - \ enzyme - \ \sim P] \ \rightarrow \ B + enzyme + ADP + phosphate\ ion$$

When the intermediate complex breaks apart, the energy is used to modify the substrate and convert it into a product of the reaction. The ADP molecule and a free phosphate ion are released into the medium and are available for recycling through cell metabolism.

Substrate Phosphorylation

ATP is generated through two mechanisms during the breakdown of glucose. A few ATP molecules are generated (that is, regenerated from ADP) as a direct result of the chemical reactions that occur in the catabolic pathways. A phosphate group is removed from an intermediate reactant in the pathway, and the free energy of the reaction is used to add the third phosphate to an available ADP molecule, producing ATP ([link]). This very direct method of phosphorylation is called **substrate-level phosphorylation**.
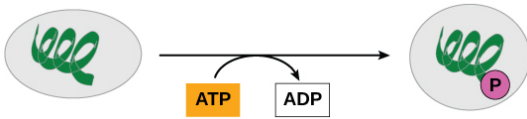
In phosphorylation reactions, the gamma phosphate of ATP is attached to a protein.

Oxidative Phosphorylation

Most of the ATP generated during glucose catabolism, however, is derived from a much more complex process, chemiosmosis, which takes place in mitochondria ([link]) within a eukaryotic cell or the plasma membrane of a prokaryotic cell. **Chemiosmosis**, a process of ATP production in cellular metabolism, is used to generate 90 percent of the ATP made during glucose catabolism and is also the method used in the light reactions of photosynthesis to harness the energy of sunlight. The production of ATP using the process of chemiosmosis is called **oxidative phosphorylation** because of the involvement of oxygen in the process.
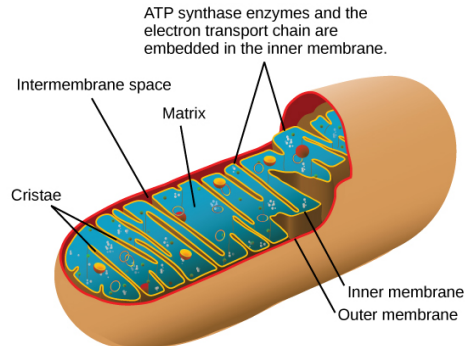
In eukaryotes, oxidative phosphorylation takes place in mitochondria. In prokaryotes, this process takes place in the plasma membrane. (Credit: modification of work by Mariana Ruiz Villareal)

Note:

Mitochondrial Disease Physician
What happens when the critical reactions of cellular respiration do not proceed correctly? Mitochondrial diseases are genetic disorders of metabolism. Mitochondrial disorders can arise from mutations in nuclear or mitochondrial DNA, and they result in the production of less energy than is normal in body cells. In type 2 diabetes, for instance, the oxidation efficiency of NADH is reduced, impacting oxidative phosphorylation but not the other steps of respiration. Symptoms of mitochondrial diseases can include muscle weakness, lack of coordination, stroke-like episodes, and loss of vision and hearing. Most affected people are diagnosed in childhood, although there are some adult-onset diseases. Identifying and treating mitochondrial disorders is a specialized medical field. The educational preparation for this profession requires a college education, followed by medical school with a specialization in medical genetics. Medical geneticists can be board certified by the American Board of Medical Genetics and go on to become associated with professional organizations devoted to the study of mitochondrial diseases, such as the Mitochondrial Medicine Society and the Society for Inherited Metabolic Disease.

Section Summary

ATP functions as the energy currency for cells. It allows the cell to store energy briefly and transport it within the cell to support endergonic chemical reactions. The structure of ATP is that of an RNA nucleotide with three phosphates attached. As ATP is used for energy, a phosphate group or two are detached, and either ADP or AMP is produced. Energy derived from glucose catabolism is used to convert ADP into ATP. When ATP is used in a reaction, the third phosphate is temporarily attached to a substrate in a process called phosphorylation. The two processes of ATP regeneration that are used in conjunction with glucose catabolism are substrate-level phosphorylation and oxidative phosphorylation through the process of chemiosmosis.

Review Questions

Exercise:

Problem: The energy currency used by cells is _____.

 a. ATP
 b. ADP
 c. AMP
 d. adenosine

Solution:

 A

Exercise:

Problem:A reducing chemical reaction _____.

a. reduces the compound to a simpler form
b. adds an electron to the substrate
c. removes a hydrogen atom from the substrate
d. is a catabolic reaction

Solution:

B

Free Response

Exercise:

Problem:

Why is it beneficial for cells to use ATP rather than energy directly from the bonds of carbohydrates? What are the greatest drawbacks to harnessing energy directly from the bonds of several different compounds?

Solution:

ATP provides the cell with a way to handle energy in an efficient manner. The molecule can be charged, stored, and used as needed. Moreover, the energy from hydrolyzing ATP is delivered as a consistent amount. Harvesting energy from the bonds of several different compounds would result in energy deliveries of different quantities.

Glossary

chemiosmosis
   process in which there is a production of adenosine triphosphate (ATP) in cellular metabolism by the involvement of a proton gradient across a membrane

dephosphorylation
   removal of a phosphate group from a molecule

oxidative phosphorylation
   production of ATP using the process of chemiosmosis and oxygen

phosphorylation
   addition of a high-energy phosphate to a compound, usually a metabolic intermediate, a protein, or ADP

redox reaction
   chemical reaction that consists of the coupling of an oxidation reaction and a reduction reaction

substrate-level phosphorylation

production of ATP from ADP using the excess energy from a chemical reaction and a phosphate group from a reactant

Glycolysis
By the end of this section, you will be able to:

- Describe the overall result in terms of molecules produced in the breakdown of glucose by glycolysis
- Compare the output of glycolysis in terms of ATP molecules and NADH molecules produced

You have read that nearly all of the energy used by living cells comes to them in the bonds of the sugar, glucose. **Glycolysis** is the first step in the breakdown of glucose to extract energy for cellular metabolism. Nearly all living organisms carry out glycolysis as part of their metabolism. The process does not use oxygen and is therefore **anaerobic**. Glycolysis takes place in the cytoplasm of both prokaryotic and eukaryotic cells. Glucose enters heterotrophic cells in two ways. One method is through secondary active transport in which the transport takes place against the glucose concentration gradient. The other mechanism uses a group of integral proteins called GLUT proteins, also known as glucose transporter proteins. These transporters assist in the facilitated diffusion of glucose.

Glycolysis begins with the six carbon ring-shaped structure of a single glucose molecule and ends with two molecules of a three-carbon sugar called **pyruvate**. Glycolysis consists of two distinct phases. The first part of the glycolysis pathway traps the glucose molecule in the cell and uses energy to modify it so that the six-carbon sugar molecule can be split evenly into the two three-carbon molecules. The second part of glycolysis extracts energy from the molecules and stores it in the form of ATP and NADH, the reduced form of NAD.

First Half of Glycolysis (Energy-Requiring Steps)

Step 1. The first step in glycolysis ([link]) is catalyzed by hexokinase, an enzyme with broad specificity that catalyzes the phosphorylation of six-carbon sugars. Hexokinase phosphorylates glucose using ATP as the source of the phosphate, producing glucose-6-phosphate, a more reactive form of glucose. This reaction prevents the phosphorylated glucose molecule from continuing to interact with the GLUT proteins, and it can no longer leave

the cell because the negatively charged phosphate will not allow it to cross the hydrophobic interior of the plasma membrane.

Step 2. In the second step of glycolysis, an isomerase converts glucose-6-phosphate into one of its isomers, fructose-6-phosphate. An **isomerase** is an enzyme that catalyzes the conversion of a molecule into one of its isomers. (This change from phosphoglucose to phosphofructose allows the eventual split of the sugar into two three-carbon molecules.).

Step 3. The third step is the phosphorylation of fructose-6-phosphate, catalyzed by the enzyme phosphofructokinase. A second ATP molecule donates a high-energy phosphate to fructose-6-phosphate, producing fructose-1,6-bisphosphate. In this pathway, phosphofructokinase is a rate-limiting enzyme. It is active when the concentration of ADP is high; it is less active when ADP levels are low and the concentration of ATP is high. Thus, if there is "sufficient" ATP in the system, the pathway slows down. This is a type of end product inhibition, since ATP is the end product of glucose catabolism.

Step 4. The newly added high-energy phosphates further destabilize fructose-1,6-bisphosphate. The fourth step in glycolysis employs an enzyme, aldolase, to cleave 1,6-bisphosphate into two three-carbon isomers: dihydroxyacetone-phosphate and glyceraldehyde-3-phosphate.

Step 5. In the fifth step, an isomerase transforms the dihydroxyacetone-phosphate into its isomer, glyceraldehyde-3-phosphate. Thus, the pathway will continue with two molecules of a single isomer. At this point in the pathway, there is a net investment of energy from two ATP molecules in the breakdown of one glucose molecule.
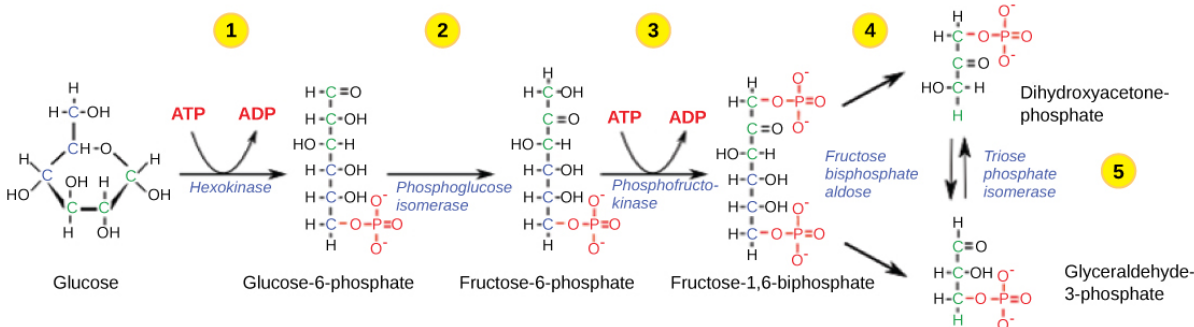
The first half of glycolysis uses two ATP molecules in the phosphorylation of glucose, which is then split into two three-carbon molecules.

Second Half of Glycolysis (Energy-Releasing Steps)

So far, glycolysis has cost the cell two ATP molecules and produced two small, three-carbon sugar molecules. Both of these molecules will proceed through the second half of the pathway, and sufficient energy will be extracted to pay back the two ATP molecules used as an initial investment and produce a profit for the cell of two additional ATP molecules and two even higher-energy NADH molecules.

Step 6. The sixth step in glycolysis ([link]) oxidizes the sugar (glyceraldehyde-3-phosphate), extracting high-energy electrons, which are picked up by the electron carrier NAD$^+$, producing NADH. The sugar is then phosphorylated by the addition of a second phosphate group, producing 1,3-bisphosphoglycerate. Note that the second phosphate group does not require another ATP molecule.
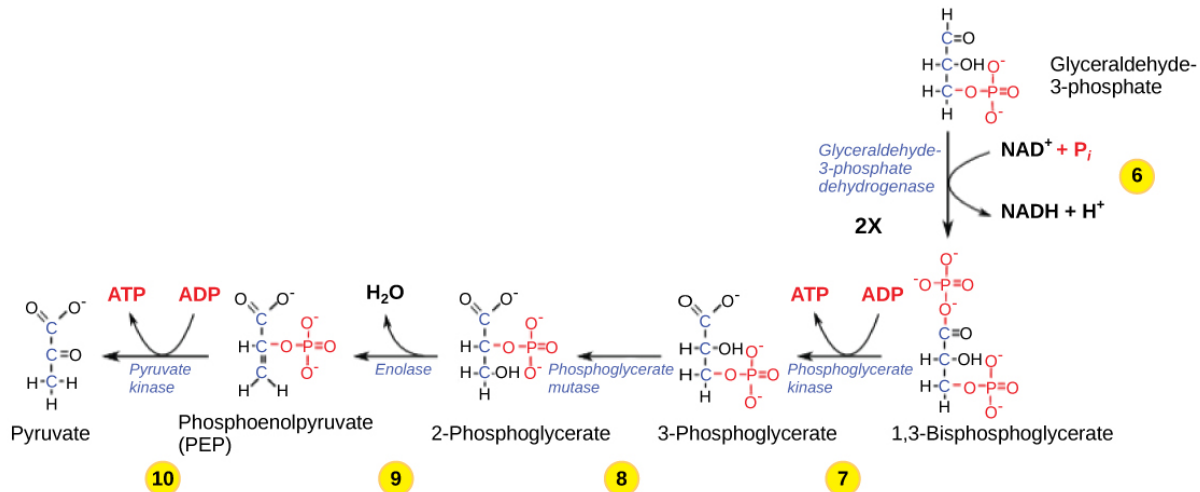
The second half of glycolysis involves phosphorylation without ATP investment (step 6) and produces two NADH and four ATP molecules per glucose.

Here again is a potential limiting factor for this pathway. The continuation of the reaction depends upon the availability of the oxidized form of the electron carrier, NAD^+. Thus, NADH must be continuously oxidized back into NAD^+ in order to keep this step going. If NAD^+ is not available, the second half of glycolysis slows down or stops. If oxygen is available in the system, the NADH will be oxidized readily, though indirectly, and the high-energy electrons from the hydrogen released in this process will be used to produce ATP. In an environment without oxygen, an alternate pathway (fermentation) can provide the oxidation of NADH to NAD^+.

Step 7. In the seventh step, catalyzed by phosphoglycerate kinase (an enzyme named for the reverse reaction), 1,3-bisphosphoglycerate donates a high-energy phosphate to ADP, forming one molecule of ATP. (This is an example of substrate-level phosphorylation.) A carbonyl group on the 1,3-bisphosphoglycerate is oxidized to a carboxyl group, and 3-phosphoglycerate is formed.

Step 8. In the eighth step, the remaining phosphate group in 3-phosphoglycerate moves from the third carbon to the second carbon,

producing 2-phosphoglycerate (an isomer of 3-phosphoglycerate). The enzyme catalyzing this step is a mutase (isomerase).

Step 9. Enolase catalyzes the ninth step. This enzyme causes 2-phosphoglycerate to lose water from its structure; this is a dehydration reaction, resulting in the formation of a double bond that increases the potential energy in the remaining phosphate bond and produces phosphoenolpyruvate (PEP).

Step 10. The last step in glycolysis is catalyzed by the enzyme pyruvate kinase (the enzyme in this case is named for the reverse reaction of pyruvate's conversion into PEP) and results in the production of a second ATP molecule by substrate-level phosphorylation and the compound pyruvic acid (or its salt form, pyruvate). Many enzymes in enzymatic pathways are named for the reverse reactions, since the enzyme can catalyze both forward and reverse reactions (these may have been described initially by the reverse reaction that takes place in vitro, under non-physiological conditions).

Outcomes of Glycolysis

Glycolysis starts with glucose and ends with two pyruvate molecules, a total of four ATP molecules and two molecules of NADH. Two ATP molecules were used in the first half of the pathway to prepare the six-carbon ring for cleavage, so the cell has a net gain of two ATP molecules and 2 NADH molecules for its use. If the cell cannot catabolize the pyruvate molecules further, it will harvest only two ATP molecules from one molecule of glucose. Mature mammalian red blood cells are not capable of **aerobic respiration**—the process in which organisms convert energy in the presence of oxygen—and glycolysis is their sole source of ATP. If glycolysis is interrupted, these cells lose their ability to maintain their sodium-potassium pumps, and eventually, they die.

The last step in glycolysis will not occur if pyruvate kinase, the enzyme that catalyzes the formation of pyruvate, is not available in sufficient quantities. In this situation, the entire glycolysis pathway will proceed, but only two ATP molecules will be made in the second half. Thus, pyruvate kinase is a rate-limiting enzyme for glycolysis.

Section Summary

Glycolysis is the first pathway used in the breakdown of glucose to extract energy. It was probably one of the earliest metabolic pathways to evolve and is used by nearly all of the organisms on earth. Glycolysis consists of two parts: The first part prepares the six-carbon ring of glucose for cleavage into two three-carbon sugars. ATP is invested in the process during this half to energize the separation. The second half of glycolysis extracts ATP and high-energy electrons from hydrogen atoms and attaches them to NAD^+. Two ATP molecules are invested in the first half and four ATP molecules are formed by substrate phosphorylation during the second half. This produces a net gain of two ATP and two NADH molecules for the cell.

Review Questions

Exercise:

Problem: During the second half of glycolysis, what occurs?

a. ATP is used up.
b. Fructose is split in two.
c. ATP is made.
d. Glucose becomes fructose.

Solution:

C

Free Response

Exercise:

Problem:

Nearly all organisms on earth carry out some form of glycolysis. How does that fact support or not support the assertion that glycolysis is one of the oldest metabolic pathways?

Solution:

If glycolysis evolved relatively late, it likely would not be as universal in organisms as it is. It probably evolved in very primitive organisms and persisted, with the addition of other pathways of carbohydrate metabolism that evolved later.

Exercise:

Problem:

Red blood cells do not perform aerobic respiration, but they do perform glycolysis. Why do all cells need an energy source, and what would happen if glycolysis were blocked in a red blood cell?

Solution:

All cells must consume energy to carry out basic functions, such as pumping ions across membranes. A red blood cell would lose its

membrane potential if glycolysis were blocked, and it would eventually die.

Glossary

aerobic respiration
    process in which organisms convert energy in the presence of oxygen

anaerobic
    process that does not use oxygen

glycolysis
    process of breaking glucose into two three-carbon molecules with the production of ATP and NADH

isomerase
    enzyme that converts a molecule into its isomer

pyruvate
    three-carbon sugar that can be decarboxylated and oxidized to make acetyl CoA, which enters the citric acid cycle under aerobic conditions; the end product of glycolysis

Oxidation of Pyruvate and the Citric Acid Cycle
By the end of this section, you will be able to:

- Explain how a circular pathway, such as the citric acid cycle, fundamentally differs from a linear pathway, such as glycolysis
- Describe how pyruvate, the product of glycolysis, is prepared for entry into the citric acid cycle

If oxygen is available, aerobic respiration will go forward. In eukaryotic cells, the pyruvate molecules produced at the end of glycolysis are transported into mitochondria, which are the sites of cellular respiration. There, pyruvate will be transformed into an acetyl group that will be picked up and activated by a carrier compound called coenzyme A (CoA). The resulting compound is called **acetyl CoA**. CoA is made from vitamin B5, pantothenic acid. Acetyl CoA can be used in a variety of ways by the cell, but its major function is to deliver the acetyl group derived from pyruvate to the next stage of the pathway in glucose catabolism.

Breakdown of Pyruvate

In order for pyruvate, the product of glycolysis, to enter the next pathway, it must undergo several changes. The conversion is a three-step process ([link]).

Step 1. A carboxyl group is removed from pyruvate, releasing a molecule of carbon dioxide into the surrounding medium. The result of this step is a two-carbon hydroxyethyl group bound to the enzyme (pyruvate dehydrogenase). This is the first of the six carbons from the original glucose molecule to be removed. This step proceeds twice (remember: there are *two* pyruvate molecules produced at the end of glycolsis) for every molecule of glucose metabolized; thus, two of the six carbons will have been removed at the end of both steps.

Step 2. The hydroxyethyl group is oxidized to an acetyl group, and the electrons are picked up by NAD^+, forming NADH. The high-energy electrons from NADH will be used later to generate ATP.

Step 3. The enzyme-bound acetyl group is transferred to CoA, producing a molecule of acetyl CoA.

Oxidation of Pyruvate		
1 O^-	CoA–SH	**3** S—CoA
$\|$		$\|$
C=O	**2**	C=O
$\|$		$\|$
C=O	NAD^+ NADH	CH_3
$\|$	+	
CH_3	CO_2	
Pyruvate	Oxidation reaction	Acetyl CoA
1	**2**	**3**
A carboxyl group is removed from pyruvate, releasing carbon dioxide.	NAD^+ is reduced to NADH.	An acetyl group is transferred to coenzyme A, resulting in acetyl CoA.

Upon entering the mitochondrial matrix, a multi-enzyme complex converts pyruvate into acetyl CoA. In the process, carbon dioxide is released and one molecule of NADH is formed.

Note that during the second stage of glucose metabolism, whenever a carbon atom is removed, it is bound to two oxygen atoms, producing carbon dioxide, one of the major end products of cellular respiration.

Acetyl CoA to CO_2

In the presence of oxygen, acetyl CoA delivers its acetyl group to a four-carbon molecule, oxaloacetate, to form citrate, a six-carbon molecule with three carboxyl groups; this pathway will harvest the remainder of the

extractable energy from what began as a glucose molecule. This single pathway is called by different names: the **citric acid cycle** (for the first intermediate formed—citric acid, or citrate—when acetate joins to the oxaloacetate), the **TCA cycle** (since citric acid or citrate and isocitrate are tricarboxylic acids), and the **Krebs cycle**, after Hans Krebs, who first identified the steps in the pathway in the 1930s in pigeon flight muscles.

Citric Acid Cycle

Like the conversion of pyruvate to acetyl CoA, the citric acid cycle takes place in the matrix of mitochondria. Almost all of the enzymes of the citric acid cycle are soluble, with the single exception of the enzyme succinate dehydrogenase, which is embedded in the inner membrane of the mitochondrion. Unlike glycolysis, the citric acid cycle is a closed loop: The last part of the pathway regenerates the compound used in the first step. The eight steps of the cycle are a series of redox, dehydration, hydration, and decarboxylation reactions that produce two carbon dioxide molecules, one GTP/ATP, and reduced forms of NADH and $FADH_2$ ([link]). This is considered an aerobic pathway because the NADH and $FADH_2$ produced must transfer their electrons to the next pathway in the system, which will use oxygen. If this transfer does not occur, the oxidation steps of the citric acid cycle also do not occur. Note that the citric acid cycle produces very little ATP directly and does not directly consume oxygen.

O   CoA
‖ |
$CH_3 - C - S$

Acetyl CoA

COO^-
|
$O = C$
|
CH_2
|
COO^-

C_4

Oxaloacetate

C_2

H_2O
SH-CoA

COO^-
|
CH_2
|
$HO - C - COO^-$
|
CH_2
|
COO^-

C_6

Citrate

NADH/H⁺

NAD⁺

COO^-
|
$HO - CH$
|
CH_2
|
COO^-

C_4

Malate

COO^-
|
CH_2
|
$HC - COO^-$
|
$HO - CH$
|
COO^-

C_6

Isocitrate

NAD⁺
NADH/H⁺
CO_2

H_2O

C_4

Fumarate

COO^-
|
CH
‖
HC
|
COO^-

C_5

α-Ketoglutarate

COO^-
|
CH_2
|
CH_2
|
$C = O$
|
COO^-

[FADH₂]
Q
[FAD]
QH₂

C_4

Succinate

COO^-
|
CH_2
|
CH_2
|
COO^-

GTP   Pᵢ
SH-CoA GDP

C_4

Succinyl CoA

NAD⁺
SH-CoA
NADH/H⁺
CO_2

COO^-
|
CH_2
|
CH_2
|
$C = O$
|
$S - CoA$
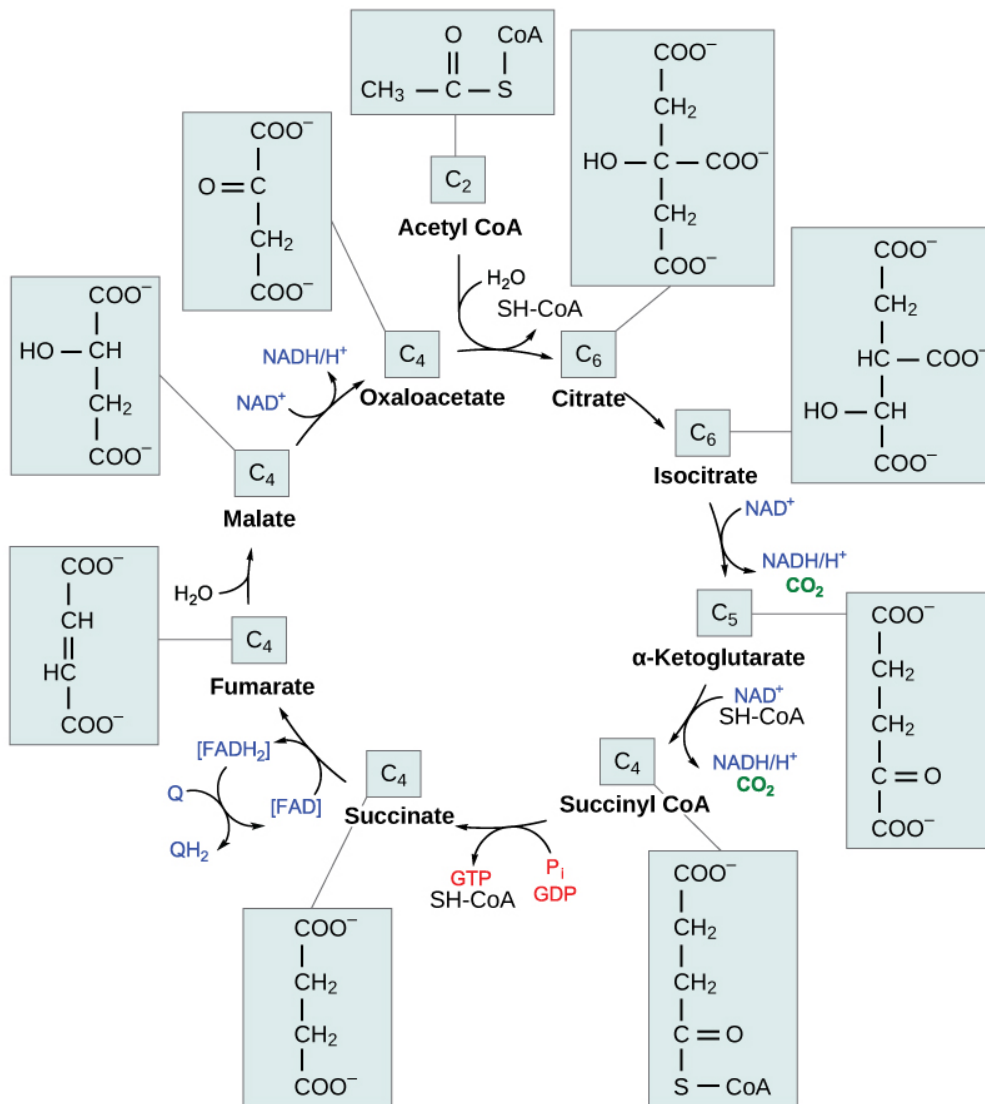
In the citric acid cycle, the acetyl group from acetyl CoA is attached to a four-carbon oxaloacetate molecule to form a six-carbon citrate molecule. Through a series of steps, citrate is oxidized, releasing two carbon dioxide molecules for each acetyl group fed into the cycle. In the process, three NAD⁺ molecules are reduced to NADH, one FAD molecule is reduced to FADH₂, and one ATP or GTP (depending on the cell type) is produced (by substrate-level phosphorylation). Because the final product of the citric acid cycle is also the first reactant, the cycle runs continuously in the presence of sufficient

reactants. (credit: modification of work by "Yikrazuul"/Wikimedia Commons)

Steps in the Citric Acid Cycle

Step 1. Prior to the start of the first step, a transitional phase occurs during which pyruvic acid is converted to acetyl CoA. Then, the first step of the cycle begins: This is a condensation step, combining the two-carbon acetyl group with a four-carbon oxaloacetate molecule to form a six-carbon molecule of citrate. CoA is bound to a sulfhydryl group (-SH) and diffuses away to eventually combine with another acetyl group. This step is irreversible because it is highly exergonic. The rate of this reaction is controlled by negative feedback and the amount of ATP available. If ATP levels increase, the rate of this reaction decreases. If ATP is in short supply, the rate increases.

Step 2. In step two, citrate loses one water molecule and gains another as citrate is converted into its isomer, isocitrate.

Step 3. In step three, isocitrate is oxidized, producing a five-carbon molecule, α-ketoglutarate, together with a molecule of CO_2 and two electrons, which reduce NAD^+ to NADH. This step is also regulated by negative feedback from ATP and NADH, and a positive effect of ADP.

Steps 3 and 4. Steps three and four are both oxidation and decarboxylation steps, which release electrons that reduce NAD^+ to NADH and release carboxyl groups that form CO_2 molecules. α-Ketoglutarate is the product of step three, and a succinyl group is the product of step four. CoA binds the succinyl group to form succinyl CoA. The enzyme that catalyzes step four is regulated by feedback inhibition of ATP, succinyl CoA, and NADH.

Step 5. In step five, a phosphate group is substituted for coenzyme A, and a high-energy bond is formed. This energy is used in substrate-level phosphorylation (during the conversion of the succinyl group to succinate) to form either guanine triphosphate (GTP) or ATP. There are two forms of

the enzyme, called isoenzymes, for this step, depending upon the type of animal tissue in which they are found. One form is found in tissues that use large amounts of ATP, such as heart and skeletal muscle. This form produces ATP. The second form of the enzyme is found in tissues that have a high number of anabolic pathways, such as liver. This form produces GTP. GTP is energetically equivalent to ATP; however, its use is more restricted. In particular, protein synthesis primarily uses GTP.

Step 6. Step six is a dehydration process that converts succinate into fumarate. Two hydrogen atoms are transferred to FAD, producing $FADH_2$. The energy contained in the electrons of these atoms is insufficient to reduce NAD^+ but adequate to reduce FAD. Unlike NADH, this carrier remains attached to the enzyme and transfers the electrons to the electron transport chain directly. This process is made possible by the localization of the enzyme catalyzing this step inside the inner membrane of the mitochondrion.

Step 7. Water is added to fumarate during step seven, and malate is produced. The last step in the citric acid cycle regenerates oxaloacetate by oxidizing malate. Another molecule of NADH is produced in the process.

Note:
Link to Learning

Click through each step of the citric acid cycle here.

Products of the Citric Acid Cycle

Two carbon atoms come into the citric acid cycle from each acetyl group, representing four out of the six carbons of one glucose molecule. Two carbon dioxide molecules are released on each turn of the cycle; however, these do not necessarily contain the most recently added carbon atoms. The two acetyl carbon atoms will eventually be released on later turns of the cycle; thus, all six carbon atoms from the original glucose molecule are eventually incorporated into carbon dioxide. Each turn of the cycle forms three NADH molecules and one $FADH_2$ molecule. These carriers will connect with the last portion of aerobic respiration to produce ATP molecules. One GTP or ATP is also made in each cycle. Several of the intermediate compounds in the citric acid cycle can be used in synthesizing non-essential amino acids; therefore, the cycle is amphibolic (both catabolic and anabolic).

Section Summary

In the presence of oxygen, pyruvate is transformed into an acetyl group attached to a carrier molecule of coenzyme A. The resulting acetyl CoA can enter several pathways, but most often, the acetyl group is delivered to the citric acid cycle for further catabolism. During the conversion of pyruvate into the acetyl group, a molecule of carbon dioxide and two high-energy electrons are removed. The carbon dioxide accounts for two (conversion of two pyruvate molecules) of the six carbons of the original glucose molecule. The electrons are picked up by NAD^+, and the NADH carries the electrons to a later pathway for ATP production. At this point, the glucose molecule that originally entered cellular respiration has been completely oxidized. Chemical potential energy stored within the glucose molecule has been transferred to electron carriers or has been used to synthesize a few ATPs.

The citric acid cycle is a series of redox and decarboxylation reactions that remove high-energy electrons and carbon dioxide. The electrons temporarily stored in molecules of NADH and $FADH_2$ are used to generate ATP in a subsequent pathway. One molecule of either GTP or ATP is produced by substrate-level phosphorylation on each turn of the cycle. There is no comparison of the cyclic pathway with a linear one.

Review Questions

Exercise:

Problem:

What is removed from pyruvate during its conversion into an acetyl group?

    a. oxygen
    b. ATP
    c. B vitamin
    d. carbon dioxide

Solution:

D

Exercise:

Problem: What do the electrons added to NAD^+ do?

    a. They become part of a fermentation pathway.
    b. They go to another pathway for ATP production.
    c. They energize the entry of the acetyl group into the citric acid cycle.
    d. They are converted to NADP.

Solution:

B

Exercise:

Problem:GTP or ATP is produced during the conversion of _____.

    a. isocitrate into α-ketoglutarate

b. succinyl CoA into succinate

c. fumarate into malate

d. malate into oxaloacetate

Solution:

B

Exercise:

Problem:

How many NADH molecules are produced on each turn of the citric acid cycle?

a. one

b. two

c. three

d. four

Solution:

C

Free Response

Exercise:

Problem:

What is the primary difference between a circular pathway and a linear pathway?

Solution:

In a circular pathway, the final product of the reaction is also the initial reactant. The pathway is self-perpetuating, as long as any of the

intermediates of the pathway are supplied. Circular pathways are able to accommodate multiple entry and exit points, thus being particularly well suited for amphibolic pathways. In a linear pathway, one trip through the pathway completes the pathway, and a second trip would be an independent event.

Glossary

acetyl CoA
    combination of an acetyl group derived from pyruvic acid and coenzyme A, which is made from pantothenic acid (a B-group vitamin)

citric acid cycle
    (also, Krebs cycle) series of enzyme-catalyzed chemical reactions of central importance in all living cells

Krebs cycle
    (also, citric acid cycle) alternate name for the citric acid cycle, named after Hans Krebs who first identified the steps in the pathway in the 1930s in pigeon flight muscles; see citric acid cycle

TCA cycle
    (also, citric acid cycle) alternate name for the citric acid cycle, named after the group name for citric acid, tricarboxylic acid (TCA); see citric acid cycle

Oxidative Phosphorylation
By the end of this section, you will be able to:

- Describe how electrons move through the electron transport chain and what happens to their energy levels
- Explain how a proton (H^+) gradient is established and maintained by the electron transport chain

You have just read about two pathways in glucose catabolism—glycolysis and the citric acid cycle—that generate ATP. Most of the ATP generated during the aerobic catabolism of glucose, however, is not generated directly from these pathways. Rather, it is derived from a process that begins with moving electrons through a series of electron transporters that undergo redox reactions. This causes hydrogen ions to accumulate within the matrix space. Therefore, a concentration gradient forms in which hydrogen ions diffuse out of the matrix space by passing through ATP synthase. The current of hydrogen ions powers the catalytic action of ATP synthase, which phosphorylates ADP, producing ATP.

Electron Transport Chain

The electron transport chain ([link]) is the last component of aerobic respiration and is the only part of glucose metabolism that uses atmospheric oxygen. Oxygen continuously diffuses into plants; in animals, it enters the body through the respiratory system. Electron transport is a series of redox reactions that resemble a relay race or bucket brigade in that electrons are passed rapidly from one component to the next, to the endpoint of the chain where the electrons reduce molecular oxygen, producing water. There are four complexes composed of proteins, labeled I through IV in [link], and the aggregation of these four complexes, together with associated mobile, accessory electron carriers, is called the electron transport chain. The electron transport chain is present in multiple copies in the inner mitochondrial membrane of eukaryotes and the plasma membrane of prokaryotes.

Electron Transport Chain
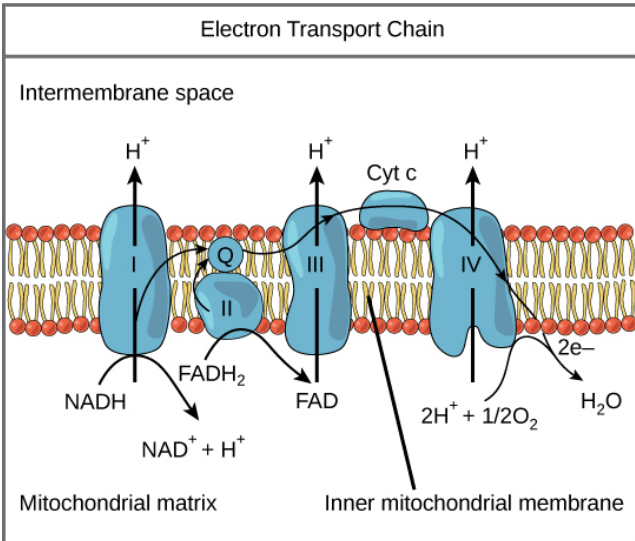
The electron transport chain is a series of electron transporters embedded in the inner mitochondrial membrane that shuttles electrons from NADH and FADH$_2$ to molecular oxygen. In the process, protons are pumped from the mitochondrial matrix to the intermembrane space, and oxygen is reduced to form water.

Complex I

To start, two electrons are carried to the first complex aboard NADH. This complex, labeled I, is composed of flavin mononucleotide (FMN) and an iron-sulfur (Fe-S)-containing protein. FMN, which is derived from vitamin B$_2$, also called riboflavin, is one of several prosthetic groups or co-factors in the electron transport chain. A **prosthetic group** is a non-protein molecule required for the activity of a protein. Prosthetic groups are organic or inorganic, non-peptide molecules bound to a protein that facilitate its function; prosthetic groups include co-enzymes, which are the prosthetic

groups of enzymes. The enzyme in complex I is NADH dehydrogenase and is a very large protein, containing 45 amino acid chains. Complex I can pump four hydrogen ions across the membrane from the matrix into the intermembrane space, and it is in this way that the hydrogen ion gradient is established and maintained between the two compartments separated by the inner mitochondrial membrane.

Q and Complex II

Complex II directly receives $FADH_2$, which does not pass through complex I. The compound connecting the first and second complexes to the third is **ubiquinone** (Q). The Q molecule is lipid soluble and freely moves through the hydrophobic core of the membrane. Once it is reduced, (QH_2), ubiquinone delivers its electrons to the next complex in the electron transport chain. Q receives the electrons derived from NADH from complex I and the electrons derived from $FADH_2$ from complex II, including succinate dehydrogenase. This enzyme and $FADH_2$ form a small complex that delivers electrons directly to the electron transport chain, bypassing the first complex. Since these electrons bypass and thus do not energize the proton pump in the first complex, fewer ATP molecules are made from the $FADH_2$ electrons. The number of ATP molecules ultimately obtained is directly proportional to the number of protons pumped across the inner mitochondrial membrane.

Complex III

The third complex is composed of cytochrome b, another Fe-S protein, Rieske center (2Fe-2S center), and cytochrome c proteins; this complex is also called cytochrome oxidoreductase. Cytochrome proteins have a prosthetic group of heme. The heme molecule is similar to the heme in hemoglobin, but it carries electrons, not oxygen. As a result, the iron ion at its core is reduced and oxidized as it passes the electrons, fluctuating between different oxidation states: Fe^{++} (reduced) and Fe^{+++} (oxidized). The heme molecules in the cytochromes have slightly different

characteristics due to the effects of the different proteins binding them, giving slightly different characteristics to each complex. Complex III pumps protons through the membrane and passes its electrons to cytochrome c for transport to the fourth complex of proteins and enzymes (cytochrome c is the acceptor of electrons from Q; however, whereas Q carries pairs of electrons, cytochrome c can accept only one at a time).

Complex IV

The fourth complex is composed of cytochrome proteins c, a, and a_3. This complex contains two heme groups (one in each of the two cytochromes, a, and a_3) and three copper ions (a pair of Cu_A and one Cu_B in cytochrome a_3). The cytochromes hold an oxygen molecule very tightly between the iron and copper ions until the oxygen is completely reduced. The reduced oxygen then picks up two hydrogen ions from the surrounding medium to make water (H_2O). The removal of the hydrogen ions from the system contributes to the ion gradient used in the process of chemiosmosis.

Chemiosmosis

In chemiosmosis, the free energy from the series of redox reactions just described is used to pump hydrogen ions (protons) across the membrane. The uneven distribution of H^+ ions across the membrane establishes both concentration and electrical gradients (thus, an electrochemical gradient), owing to the hydrogen ions' positive charge and their aggregation on one side of the membrane.

If the membrane were open to diffusion by the hydrogen ions, the ions would tend to diffuse back across into the matrix, driven by their electrochemical gradient. Recall that many ions cannot diffuse through the nonpolar regions of phospholipid membranes without the aid of ion channels. Similarly, hydrogen ions in the matrix space can only pass through the inner mitochondrial membrane through an integral membrane protein called ATP synthase ([link]). This complex protein acts as a tiny generator, turned by the force of the hydrogen ions diffusing through it,

down their electrochemical gradient. The turning of parts of this molecular machine facilitates the addition of a phosphate to ADP, forming ATP, using the potential energy of the hydrogen ion gradient.
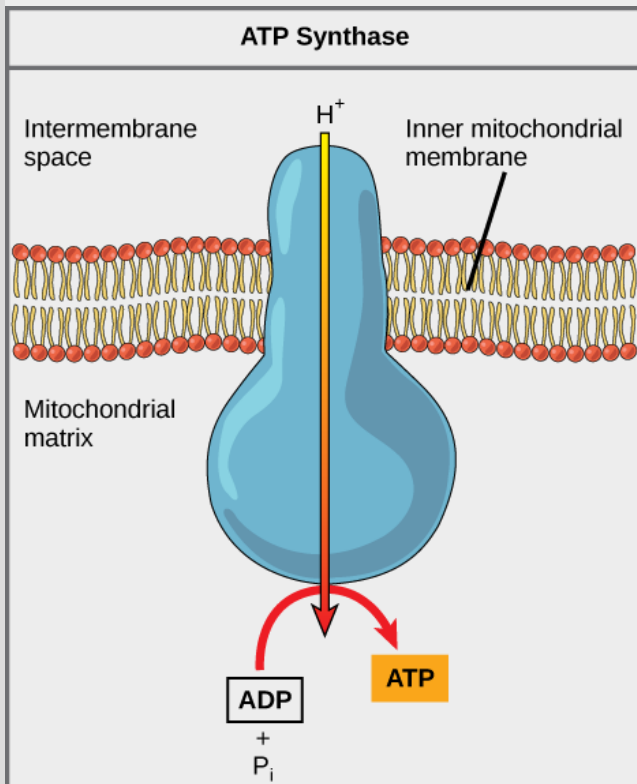
ATP synthase is a complex, molecular machine that uses a proton (H^+) gradient to form ATP from ADP and inorganic phosphate (Pi). (Credit: modification of work by Klaus Hoffmeier)

Dinitrophenol (DNP) is an uncoupler that makes the inner mitochondrial membrane leaky to protons. It was used until 1938 as a weight-loss drug.

> What effect would you expect DNP to have on the change in pH across the inner mitochondrial membrane? Why do you think this might be an effective weight-loss drug?

Chemiosmosis ([link]) is used to generate 90 percent of the ATP made during aerobic glucose catabolism; it is also the method used in the light reactions of photosynthesis to harness the energy of sunlight in the process of photophosphorylation. Recall that the production of ATP using the process of chemiosmosis in mitochondria is called oxidative phosphorylation. The overall result of these reactions is the production of ATP from the energy of the electrons removed from hydrogen atoms. These atoms were originally part of a glucose molecule. At the end of the pathway, the electrons are used to reduce an oxygen molecule to oxygen ions. The extra electrons on the oxygen attract hydrogen ions (protons) from the surrounding medium, and water is formed.

Note:
Art Connection
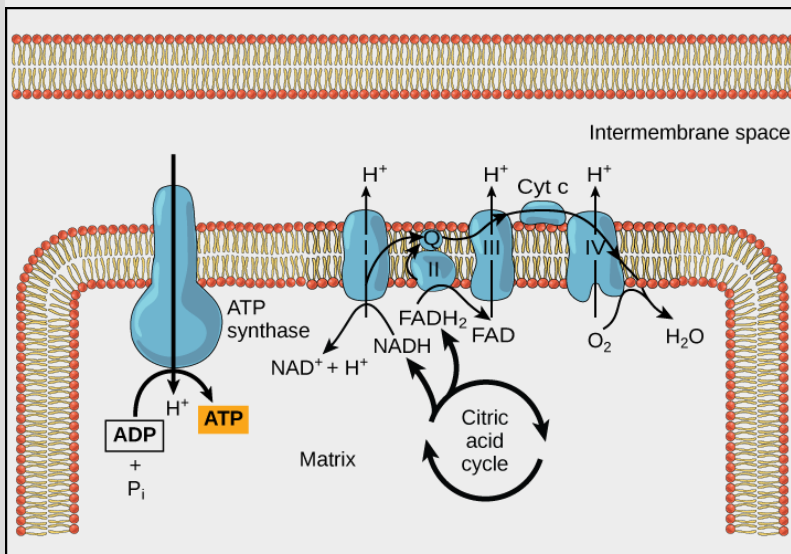
In oxidative phosphorylation, the pH gradient formed by the electron transport

chain is used by ATP synthase to form ATP.

Cyanide inhibits cytochrome c oxidase, a component of the electron transport chain. If cyanide poisoning occurs, would you expect the pH of the intermembrane space to increase or decrease? What effect would cyanide have on ATP synthesis?

ATP Yield

The number of ATP molecules generated from the catabolism of glucose varies. For example, the number of hydrogen ions that the electron transport chain complexes can pump through the membrane varies between species. Another source of variance stems from the shuttle of electrons across the membranes of the mitochondria. (The NADH generated from glycolysis cannot easily enter mitochondria.) Thus, electrons are picked up on the inside of mitochondria by either NAD^+ or FAD^+. As you have learned earlier, these FAD^+ molecules can transport fewer ions; consequently, fewer ATP molecules are generated when FAD^+ acts as a carrier. NAD^+ is used as the electron transporter in the liver and FAD^+ acts in the brain.

Another factor that affects the yield of ATP molecules generated from glucose is the fact that intermediate compounds in these pathways are used for other purposes. Glucose catabolism connects with the pathways that build or break down all other biochemical compounds in cells, and the result is somewhat messier than the ideal situations described thus far. For example, sugars other than glucose are fed into the glycolytic pathway for energy extraction. Moreover, the five-carbon sugars that form nucleic acids are made from intermediates in glycolysis. Certain nonessential amino acids can be made from intermediates of both glycolysis and the citric acid cycle. Lipids, such as cholesterol and triglycerides, are also made from intermediates in these pathways, and both amino acids and triglycerides are broken down for energy through these pathways. Overall, in living systems, these pathways of glucose catabolism extract about 34 percent of the energy contained in glucose.

Section Summary

The electron transport chain is the portion of aerobic respiration that uses free oxygen as the final electron acceptor of the electrons removed from the intermediate compounds in glucose catabolism. The electron transport chain is composed of four large, multiprotein complexes embedded in the inner mitochondrial membrane and two small diffusible electron carriers shuttling electrons between them. The electrons are passed through a series of redox reactions, with a small amount of free energy used at three points to transport hydrogen ions across a membrane. This process contributes to the gradient used in chemiosmosis. The electrons passing through the electron transport chain gradually lose energy, High-energy electrons donated to the chain by either NADH or $FADH_2$ complete the chain, as low-energy electrons reduce oxygen molecules and form water. The level of free energy of the electrons drops from about 60 kcal/mol in NADH or 45 kcal/mol in $FADH_2$ to about 0 kcal/mol in water. The end products of the electron transport chain are water and ATP. A number of intermediate compounds of the citric acid cycle can be diverted into the anabolism of other biochemical molecules, such as nonessential amino acids, sugars, and lipids. These same molecules can serve as energy sources for the glucose pathways.

Art Connections

Exercise:

Problem:

[link] Dinitrophenol (DNP) is an uncoupler that makes the inner mitochondrial membrane leaky to protons. It was used until 1938 as a weight-loss drug. What effect would you expect DNP to have on the change in pH across the inner mitochondrial membrane? Why do you think this might be an effective weight-loss drug?

Solution:

[link] After DNP poisoning, the electron transport chain can no longer form a proton gradient, and ATP synthase can no longer make ATP. DNP is an effective diet drug because it uncouples ATP synthesis; in

other words, after taking it, a person obtains less energy out of the food he or she eats. Interestingly, one of the worst side effects of this drug is hyperthermia, or overheating of the body. Since ATP cannot be formed, the energy from electron transport is lost as heat.

Exercise:

Problem:

[link] Cyanide inhibits cytochrome c oxidase, a component of the electron transport chain. If cyanide poisoning occurs, would you expect the pH of the intermembrane space to increase or decrease? What effect would cyanide have on ATP synthesis?

Solution:

[link] After cyanide poisoning, the electron transport chain can no longer pump electrons into the intermembrane space. The pH of the intermembrane space would increase, the pH gradient would decrease, and ATP synthesis would stop.

Review Questions

Exercise:

Problem: What compound receives electrons from NADH?

    a. FMN
    b. ubiquinone
    c. cytochrome c_1
    d. oxygen

Solution:

A

Exercise:

Problem: Chemiosmosis involves _____.

    a. the movement of electrons across the cell membrane
    b. the movement of hydrogen atoms across a mitochondrial membrane
    c. the movement of hydrogen ions across a mitochondrial membrane
    d. the movement of glucose through the cell membrane

Solution:

C

Free Response

Exercise:

Problem:

How do the roles of ubiquinone and cytochrome c differ from the other components of the electron transport chain?

Solution:

Q and cytochrome c are transport molecules. Their function does not result directly in ATP synthesis in that they are not pumps. Moreover, Q is the only component of the electron transport chain that is not a protein. Ubiquinone and cytochrome c are small, mobile, electron carriers, whereas the other components of the electron transport chain are large complexes anchored in the inner mitochondrial membrane.

Exercise:

Problem:

What accounts for the different number of ATP molecules that are formed through cellular respiration?

Solution:

Few tissues except muscle produce the maximum possible amount of ATP from nutrients. The intermediates are used to produce needed amino acids, fatty acids, cholesterol, and sugars for nucleic acids. When NADH is transported from the cytoplasm to the mitochondria, an active transport mechanism is used, which decreases the amount of ATP that can be made. The electron transport chain differs in composition between species, so different organisms will make different amounts of ATP using their electron transport chains.

Glossary

ATP synthase
    (also, F1F0 ATP synthase) membrane-embedded protein complex that adds a phosphate to ADP with energy from protons diffusing through it

prosthetic group
    (also, prosthetic cofactor) molecule bound to a protein that facilitates the function of the protein

ubiquinone
    soluble electron transporter in the electron transport chain that connects the first or second complex to the third

Metabolism without Oxygen
By the end of this section, you will be able to:

- Discuss the fundamental difference between anaerobic cellular respiration and fermentation
- Describe the type of fermentation that readily occurs in animal cells and the conditions that initiate that fermentation

In aerobic respiration, the final electron acceptor is an oxygen molecule, O_2. If aerobic respiration occurs, then ATP will be produced using the energy of high-energy electrons carried by NADH or $FADH_2$ to the electron transport chain. If aerobic respiration does not occur, NADH must be reoxidized to NAD^+ for reuse as an electron carrier for the glycolytic pathway to continue. How is this done? Some living systems use an organic molecule as the final electron acceptor. Processes that use an organic molecule to regenerate NAD^+ from NADH are collectively referred to as **fermentation**. In contrast, some living systems use an inorganic molecule as a final electron acceptor. Both methods are called **anaerobic cellular respiration** in which organisms convert energy for their use in the absence of oxygen.

Anaerobic Cellular Respiration

Certain prokaryotes, including some species of bacteria and Archaea, use anaerobic respiration. For example, the group of Archaea called methanogens reduces carbon dioxide to methane to oxidize NADH. These microorganisms are found in soil and in the digestive tracts of ruminants, such as cows and sheep. Similarly, sulfate-reducing bacteria and Archaea, most of which are anaerobic ([link]), reduce sulfate to hydrogen sulfide to regenerate NAD^+ from NADH.
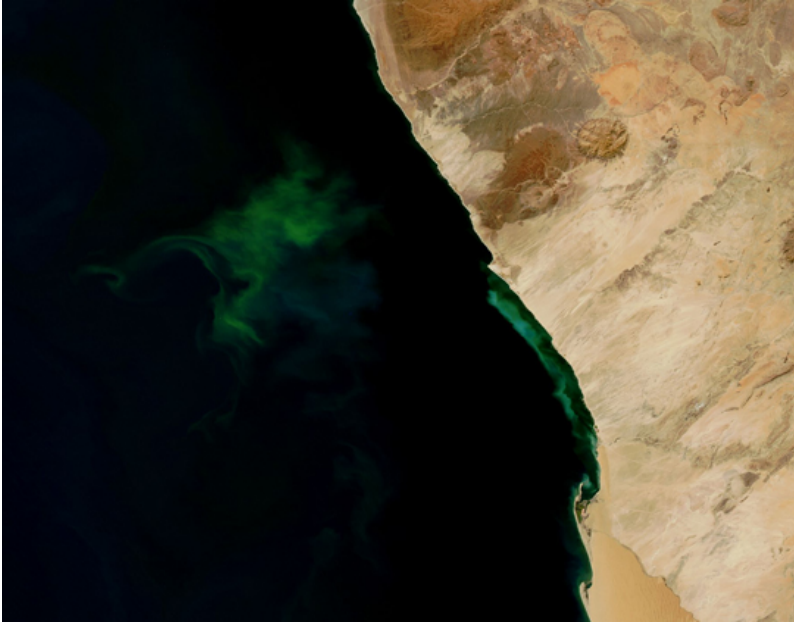
The green color seen in these coastal waters is from an eruption of hydrogen sulfide-producing bacteria. These anaerobic, sulfate-reducing bacteria release hydrogen sulfide gas as they decompose algae in the water. (credit: modification of work by NASA/Jeff Schmaltz, MODIS Land Rapid Response Team at NASA GSFC, Visible Earth Catalog of NASA images)

Note:
Link to Learning

Lactic Acid Fermentation

The fermentation method used by animals and certain bacteria, like those in yogurt, is lactic acid fermentation ([link]). This type of fermentation is used routinely in mammalian red blood cells and in skeletal muscle that has an insufficient oxygen supply to allow aerobic respiration to continue (that is, in muscles used to the point of fatigue). In muscles, lactic acid accumulation must be removed by the blood circulation and the lactate brought to the liver for further metabolism. The chemical reactions of lactic acid fermentation are the following:

Equation:

$$\text{Pyruvic acid} + \text{NADH} \leftrightarrow \text{lactic acid} + \text{NAD}^+$$
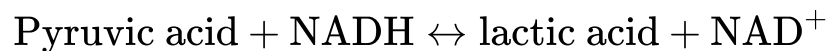
The enzyme used in this reaction is lactate dehydrogenase (LDH). The reaction can proceed in either direction, but the reaction from left to right is inhibited by acidic conditions. Such lactic acid accumulation was once believed to cause muscle stiffness, fatigue, and soreness, although more recent research disputes this hypothesis. Once the lactic acid has been removed from the muscle and circulated to the liver, it can be reconverted into pyruvic acid and further catabolized for energy.

Note:
Art Connection

Lactic Acid Fermentation

Glucose

Glycolysis

Net 2 ATP

2 NAD⁺

2 NADH

2 Pyruvate

Fermentation

2 NADH

2 NAD⁺
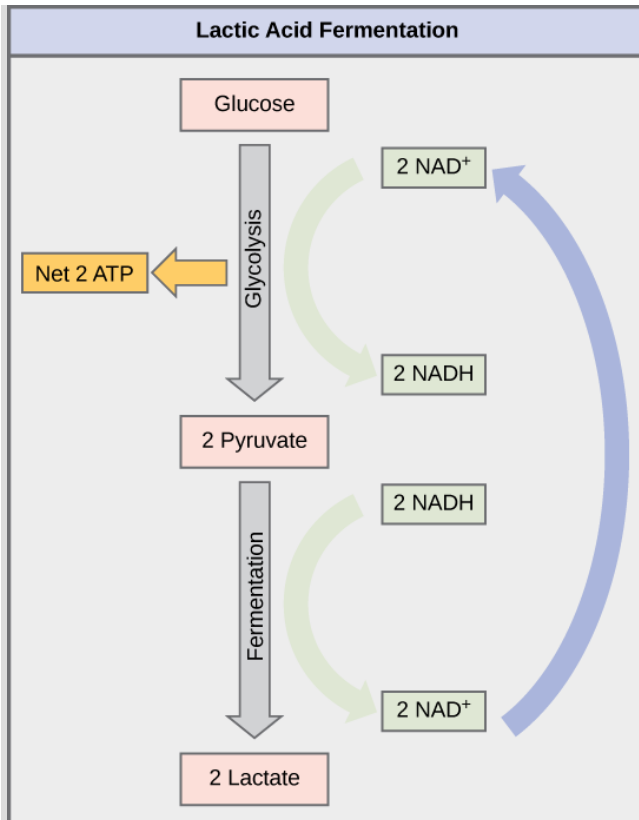
2 Lactate

Lactic acid fermentation is common in muscle cells that have run out of oxygen.

Tremetol, a metabolic poison found in the white snake root plant, prevents the metabolism of lactate. When cows eat this plant, it is concentrated in the milk they produce. Humans who consume the milk become ill. Symptoms of this disease, which include vomiting, abdominal pain, and tremors, become worse after exercise. Why do you think this is the case?

Alcohol Fermentation

Another familiar fermentation process is alcohol fermentation ([link]) that produces ethanol, an alcohol. The first chemical reaction of alcohol

fermentation is the following (CO_2 does not participate in the second reaction):

Equation:

$$\text{Pyruvic acid} \rightarrow CO_2 + \text{acetaldehyde} + \text{NADH} \rightarrow \text{ethanol} + \text{NAD}^+$$
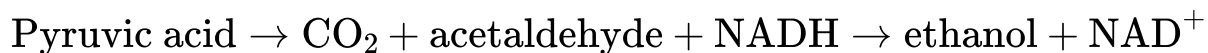
The first reaction is catalyzed by pyruvate decarboxylase, a cytoplasmic enzyme, with a coenzyme of thiamine pyrophosphate (TPP, derived from vitamin B_1 and also called thiamine). A carboxyl group is removed from pyruvic acid, releasing carbon dioxide as a gas. The loss of carbon dioxide reduces the size of the molecule by one carbon, making acetaldehyde. The second reaction is catalyzed by alcohol dehydrogenase to oxidize NADH to NAD^+ and reduce acetaldehyde to ethanol. The fermentation of pyruvic acid by yeast produces the ethanol found in alcoholic beverages. Ethanol tolerance of yeast is variable, ranging from about 5 percent to 21 percent, depending on the yeast strain and environmental conditions.

Fermentation of grape juice into wine produces CO_2 as a byproduct. Fermentation tanks have valves so that the pressure inside the tanks

created by the carbon dioxide
produced can be released.

Other Types of Fermentation

Other fermentation methods occur in bacteria. Many prokaryotes are
facultatively anaerobic. This means that they can switch between aerobic
respiration and fermentation, depending on the availability of oxygen.
Certain prokaryotes, like *Clostridia*, are obligate anaerobes. Obligate
anaerobes live and grow in the absence of molecular oxygen. Oxygen is a
poison to these microorganisms and kills them on exposure. It should be
noted that all forms of fermentation, except lactic acid fermentation,
produce gas. The production of particular types of gas is used as an
indicator of the fermentation of specific carbohydrates, which plays a role
in the laboratory identification of the bacteria. Various methods of
fermentation are used by assorted organisms to ensure an adequate supply
of NAD^+ for the sixth step in glycolysis. Without these pathways, that step
would not occur and no ATP would be harvested from the breakdown of
glucose.

Section Summary

If NADH cannot be oxidized through aerobic respiration, another electron
acceptor is used. Most organisms will use some form of fermentation to
accomplish the regeneration of NAD^+, ensuring the continuation of
glycolysis. The regeneration of NAD^+ in fermentation is not accompanied
by ATP production; therefore, the potential of NADH to produce ATP using
an electron transport chain is not utilized.

Art Connections

Exercise:

Problem:

[link] Tremetol, a metabolic poison found in the white snake root plant, prevents the metabolism of lactate. When cows eat this plant, it is concentrated in the milk they produce. Humans who consume the milk become ill. Symptoms of this disease, which include vomiting, abdominal pain, and tremors, become worse after exercise. Why do you think this is the case?

Solution:

[link] The illness is caused by lactate accumulation. Lactate levels rise after exercise, making the symptoms worse. Milk sickness is rare today, but was common in the Midwestern United States in the early 1800s.

Review Questions

Exercise:

Problem:

Which of the following fermentation methods can occur in animal skeletal muscles?

    a. lactic acid fermentation
    b. alcohol fermentation
    c. mixed acid fermentation
    d. propionic fermentation

Solution:

A

Free Response

Exercise:

Problem:

What is the primary difference between fermentation and anaerobic respiration?

Solution:

Fermentation uses glycolysis only. Anaerobic respiration uses all three parts of cellular respiration, including the parts in the mitochondria like the citric acid cycle and electron transport; it also uses a different final electron acceptor instead of oxygen gas.

Glossary

anaerobic cellular respiration
> process in which organisms convert energy for their use in the absence of oxygen

fermentation
> process of regenerating NAD^+ with either an inorganic or organic compound serving as the final electron acceptor, occurs in the absence; occurs in the absence of oxygen

Connections of Carbohydrate, Protein, and Lipid Metabolic Pathways
By the end of this section, you will be able to:

- Discuss the ways in which carbohydrate metabolic pathways, glycolysis, and the citric acid cycle interrelate with protein and lipid metabolic pathways
- Explain why metabolic pathways are not considered closed systems

You have learned about the catabolism of glucose, which provides energy to living cells. But living things consume more than glucose for food. How does a turkey sandwich end up as ATP in your cells? This happens because all of the catabolic pathways for carbohydrates, proteins, and lipids eventually connect into glycolysis and the citric acid cycle pathways (see [link]). Metabolic pathways should be thought of as porous—that is, substances enter from other pathways, and intermediates leave for other pathways. These pathways are not closed systems. Many of the substrates, intermediates, and products in a particular pathway are reactants in other pathways.

Connections of Other Sugars to Glucose Metabolism

Glycogen, a polymer of glucose, is an energy storage molecule in animals. When there is adequate ATP present, excess glucose is shunted into glycogen for storage. Glycogen is made and stored in both liver and muscle. The glycogen will be hydrolyzed into glucose monomers (G-1-P) if blood sugar levels drop. The presence of glycogen as a source of glucose allows ATP to be produced for a longer period of time during exercise. Glycogen is broken down into G-1-P and converted into G-6-P in both muscle and liver cells, and this product enters the glycolytic pathway.

Sucrose is a disaccharide with a molecule of glucose and a molecule of fructose bonded together with a glycosidic linkage. Fructose is one of the three dietary monosaccharides, along with glucose and galactose (which is part of the milk sugar, the disaccharide lactose), which are absorbed directly into the bloodstream during digestion. The catabolism of both fructose and galactose produces the same number of ATP molecules as glucose.

Connections of Proteins to Glucose Metabolism

Proteins are hydrolyzed by a variety of enzymes in cells. Most of the time, the amino acids are recycled into the synthesis of new proteins. If there are excess amino acids, however, or if the body is in a state of starvation, some amino acids will be shunted into the pathways of glucose catabolism ([link]). Each amino acid must have its amino group removed prior to entry into these pathways. The amino group is converted into ammonia. In mammals, the liver synthesizes urea from two ammonia molecules and a carbon dioxide molecule. Thus, urea is the principal waste product in mammals produced from the nitrogen originating in amino acids, and it leaves the body in urine.
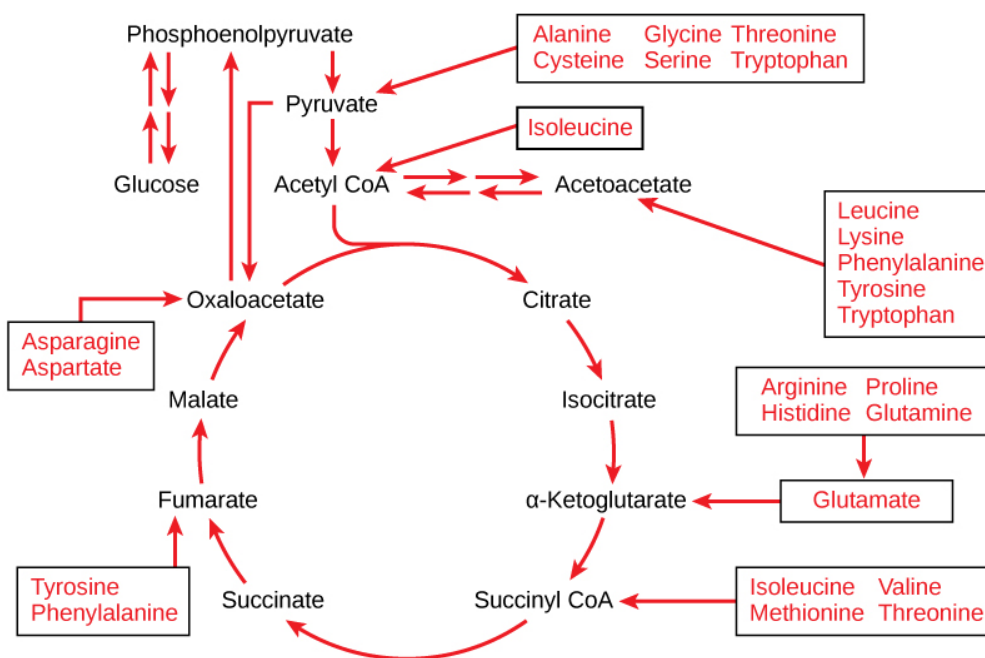
The carbon skeletons of certain amino acids (indicated in boxes) derived from proteins can feed into the citric acid cycle. (credit: modification of work by Mikael Häggström)

Connections of Lipid and Glucose Metabolisms

The lipids that are connected to the glucose pathways are cholesterol and triglycerides. Cholesterol is a lipid that contributes to cell membrane flexibility and is a precursor of steroid hormones. The synthesis of cholesterol starts with acetyl groups and proceeds in only one direction. The process cannot be reversed.

Triglycerides are a form of long-term energy storage in animals. Triglycerides are made of glycerol and three fatty acids. Animals can make most of the fatty acids they need. Triglycerides can be both made and broken down through parts of the glucose catabolism pathways. Glycerol can be phosphorylated to glycerol-3-phosphate, which continues through glycolysis. Fatty acids are catabolized in a process called beta-oxidation that takes place in the matrix of the mitochondria and converts their fatty acid chains into two carbon units of acetyl groups. The acetyl groups are picked up by CoA to form acetyl CoA that proceeds into the citric acid cycle.
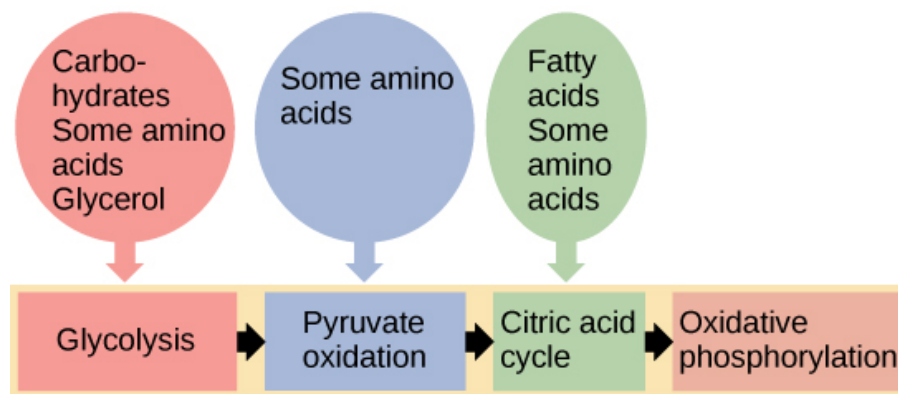
Glycogen from the liver and muscles, hydrolyzed into glucose-1-phosphate, together with fats and proteins, can feed into the catabolic pathways for carbohydrates.

Note:
Evolution Connection
Pathways of Photosynthesis and Cellular Metabolism
The processes of photosynthesis and cellular metabolism consist of several very complex pathways. It is generally thought that the first cells arose in an aqueous environment—a "soup" of nutrients—probably on the surface of some porous clays. If these cells reproduced successfully and their numbers climbed steadily, it follows that the cells would begin to deplete the nutrients from the medium in which they lived as they shifted the nutrients into the components of their own bodies. This hypothetical situation would have resulted in natural selection favoring those organisms that could exist by using the nutrients that remained in their environment and by manipulating these nutrients into materials upon which they could survive. Selection would favor those organisms that could extract maximal value from the nutrients to which they had access.
An early form of photosynthesis developed that harnessed the sun's energy using water as a source of hydrogen atoms, but this pathway did not produce free oxygen (anoxygenic photosynthesis). (Early photosynthesis did not produce free oxygen because it did not use water as the source of hydrogen ions; instead, it used materials like hydrogen sulfide and consequently produced sulfur). It is thought that glycolysis could take advantage of the simple sugars being produced, but these reactions were unable to fully extract the energy stored in the carbohydrates. The development of glycolysis probably predated the evolution of photosynthesis, as it was well suited to extract energy from materials spontaneously accumulating in the "primeval soup." A later form of photosynthesis used water as a source of electrons and hydrogen, and generated free oxygen. Over time, the atmosphere became oxygenated, but not before the oxygen released oxidized metals in the ocean and created a "rust" layer in the sediment, permitting the dating of the rise of the first oxygenic photosynthesizers. Living things adapted to exploit this new atmosphere that allowed aerobic respiration as we know it to evolve. When the full process of oxygenic photosynthesis developed and the atmosphere became oxygenated, cells were finally able to use the oxygen expelled by photosynthesis to extract considerably more energy from the sugar molecules using the citric acid cycle and oxidative phosphorylation.

Section Summary

The breakdown and synthesis of carbohydrates, proteins, and lipids connect with the pathways of glucose catabolism. The simple sugars are galactose, fructose, glycogen, and pentose. These are catabolized during glycolysis. The amino acids from proteins connect with glucose catabolism through pyruvate, acetyl CoA, and components of the citric acid cycle. Cholesterol synthesis starts with acetyl groups, and the components of triglycerides come from glycerol-3-phosphate from glycolysis and acetyl groups produced in the mitochondria from pyruvate.

Review Questions

Exercise:

Problem: A major connection for sugars in glycolysis is _____.

a. glucose-6-phosphate
b. fructose-1,6-bisphosphate
c. dihydroxyacetone phosphate
d. phosphoenolpyruvate

Solution:

A

Exercise:

Problem: Beta-oxidation is _____.

a. the breakdown of sugars
b. the assembly of sugars
c. the breakdown of fatty acids
d. the removal of amino groups from amino acids

Solution:

C

Free Response

Exercise:

Problem:

Would you describe metabolic pathways as inherently wasteful or inherently economical, and why?

Solution:

They are very economical. The substrates, intermediates, and products move between pathways and do so in response to finely tuned feedback inhibition loops that keep metabolism balanced overall. Intermediates in one pathway may occur in another, and they can move from one pathway to another fluidly in response to the needs of the cell.

Regulation of Cellular Respiration
By the end of this section, you will be able to:

- Describe how feedback inhibition would affect the production of an intermediate or product in a pathway
- Identify the mechanism that controls the rate of the transport of electrons through the electron transport chain

Cellular respiration must be regulated in order to provide balanced amounts of energy in the form of ATP. The cell also must generate a number of intermediate compounds that are used in the anabolism and catabolism of macromolecules. Without controls, metabolic reactions would quickly come to a stand still as the forward and backward reactions reached a state of equilibrium. Resources would be used inappropriately. A cell does not need the maximum amount of ATP that it can make all the time: At times, the cell needs to shunt some of the intermediates to pathways for amino acid, protein, glycogen, lipid, and nucleic acid production. In short, the cell needs to control its metabolism.

Regulatory Mechanisms

A variety of mechanisms is used to control cellular respiration. Some type of control exists at each stage of glucose metabolism. Access of glucose to the cell can be regulated using the **GLUT proteins** that transport glucose ([link]). Different forms of the GLUT protein control passage of glucose into the cells of specific tissues.

Insulin receptor   Insulin   Glucose

Glut4

Vesicle

Plasma membrane

In the presence of insulin, Glut4 vesicles fuse with the plasma membrane.

Glut4 allows glucose to enter the cell.
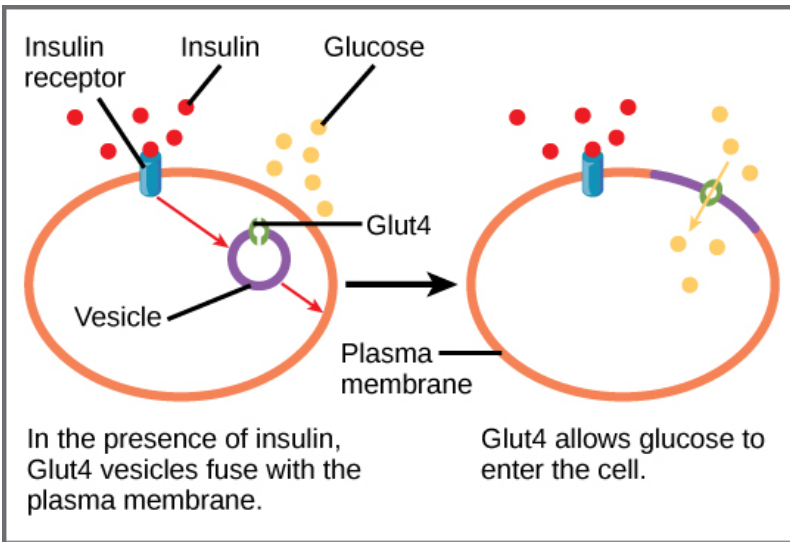
GLUT4 is a glucose transporter that is stored in vesicles. A cascade of events that occurs upon insulin binding to a receptor in the plasma membrane causes GLUT4-containing vesicles to fuse with the plasma membrane so that glucose may be transported into the cell.

Some reactions are controlled by having two different enzymes—one each for the two directions of a reversible reaction. Reactions that are catalyzed by only one enzyme can go to equilibrium, stalling the reaction. In contrast, if two different enzymes (each specific for a given direction) are necessary for a reversible reaction, the opportunity to control the rate of the reaction increases, and equilibrium is not reached.

A number of enzymes involved in each of the pathways—in particular, the enzyme catalyzing the first committed reaction of the pathway—are controlled by attachment of a molecule to an allosteric site on the protein. The molecules most commonly used in this capacity are the nucleotides ATP, ADP, AMP, NAD^+, and NADH. These regulators, allosteric effectors, may increase or decrease enzyme activity, depending on the prevailing conditions. The allosteric effector alters the steric structure of the enzyme,

usually affecting the configuration of the active site. This alteration of the protein's (the enzyme's) structure either increases or decreases its affinity for its substrate, with the effect of increasing or decreasing the rate of the reaction. The attachment signals to the enzyme. This binding can increase or decrease the enzyme's activity, providing feedback. This feedback type of control is effective as long as the chemical affecting it is attached to the enzyme. Once the overall concentration of the chemical decreases, it will diffuse away from the protein, and the control is relaxed.

Control of Catabolic Pathways

Enzymes, proteins, electron carriers, and pumps that play roles in glycolysis, the citric acid cycle, and the electron transport chain tend to catalyze non-reversible reactions. In other words, if the initial reaction takes place, the pathway is committed to proceeding with the remaining reactions. Whether a particular enzyme activity is released depends upon the energy needs of the cell (as reflected by the levels of ATP, ADP, and AMP).

Glycolysis

The control of glycolysis begins with the first enzyme in the pathway, hexokinase ([link]). This enzyme catalyzes the phosphorylation of glucose, which helps to prepare the compound for cleavage in a later step. The presence of the negatively charged phosphate in the molecule also prevents the sugar from leaving the cell. When hexokinase is inhibited, glucose diffuses out of the cell and does not become a substrate for the respiration pathways in that tissue. The product of the hexokinase reaction is glucose-6-phosphate, which accumulates when a later enzyme, phosphofructokinase, is inhibited.
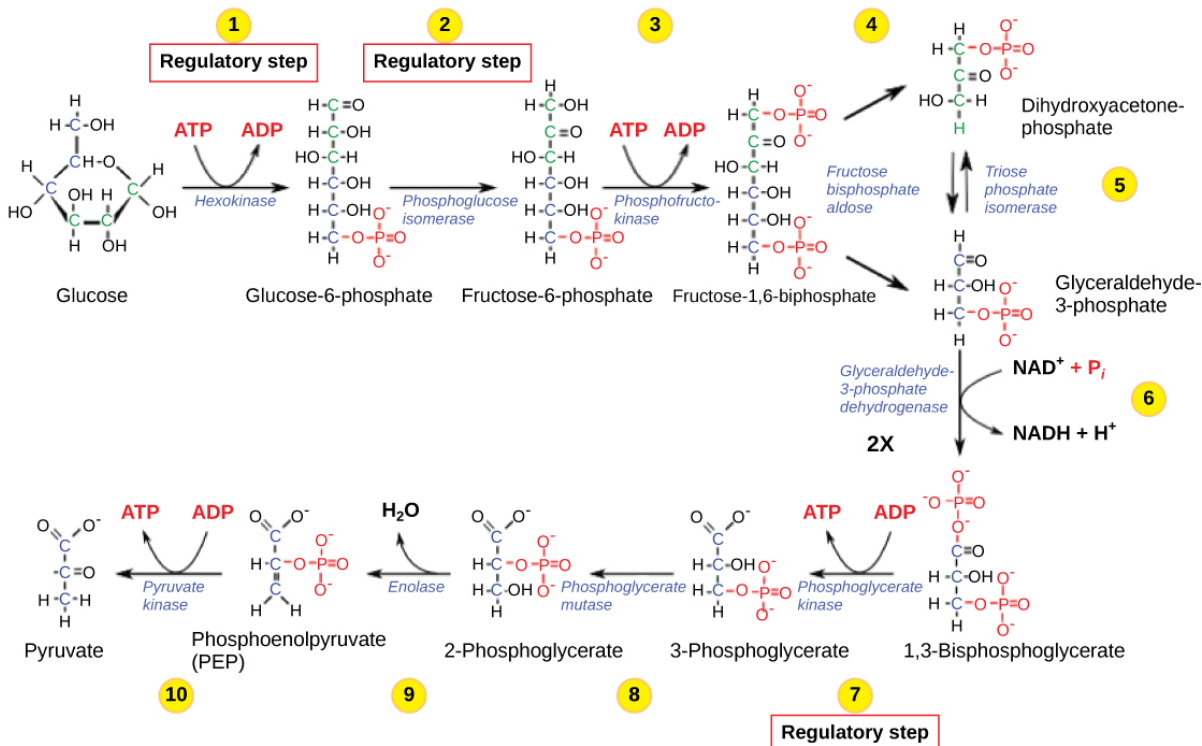
The glycolysis pathway is primarily regulated at the three key enzymatic steps (1, 2, and 7) as indicated. Note that the first two steps that are regulated occur early in the pathway and involve hydrolysis of ATP.

Phosphofructokinase is the main enzyme controlled in glycolysis. High levels of ATP, citrate, or a lower, more acidic pH decrease the enzyme's activity. An increase in citrate concentration can occur because of a blockage in the citric acid cycle. Fermentation, with its production of organic acids like lactic acid, frequently accounts for the increased acidity in a cell; however, the products of fermentation do not typically accumulate in cells.

The last step in glycolysis is catalyzed by pyruvate kinase. The pyruvate produced can proceed to be catabolized or converted into the amino acid alanine. If no more energy is needed and alanine is in adequate supply, the enzyme is inhibited. The enzyme's activity is increased when fructose-1,6-bisphosphate levels increase. (Recall that fructose-1,6-bisphosphate is an

intermediate in the first half of glycolysis.) The regulation of pyruvate kinase involves phosphorylation by a kinase (pyruvate kinase kinase), resulting in a less-active enzyme. Dephosphorylation by a phosphatase reactivates it. Pyruvate kinase is also regulated by ATP (a negative allosteric effect).

If more energy is needed, more pyruvate will be converted into acetyl CoA through the action of pyruvate dehydrogenase. If either acetyl groups or NADH accumulate, there is less need for the reaction and the rate decreases. Pyruvate dehydrogenase is also regulated by phosphorylation: A kinase phosphorylates it to form an inactive enzyme, and a phosphatase reactivates it. The kinase and the phosphatase are also regulated.

Citric Acid Cycle

The citric acid cycle is controlled through the enzymes that catalyze the reactions that make the first two molecules of NADH ([link]). These enzymes are isocitrate dehydrogenase and α-ketoglutarate dehydrogenase. When adequate ATP and NADH levels are available, the rates of these reactions decrease. When more ATP is needed, as reflected in rising ADP levels, the rate increases. α-Ketoglutarate dehydrogenase will also be affected by the levels of succinyl CoA—a subsequent intermediate in the cycle—causing a decrease in activity. A decrease in the rate of operation of the pathway at this point is not necessarily negative, as the increased levels of the α-ketoglutarate not used by the citric acid cycle can be used by the cell for amino acid (glutamate) synthesis.

Electron Transport Chain

Specific enzymes of the electron transport chain are unaffected by feedback inhibition, but the rate of electron transport through the pathway is affected by the levels of ADP and ATP. Greater ATP consumption by a cell is indicated by a buildup of ADP. As ATP usage decreases, the concentration of ADP decreases, and now, ATP begins to build up in the cell. This change

is the relative concentration of ADP to ATP triggers the cell to slow down the electron transport chain.

For a summary of feedback controls in cellular respiration, see [link].

Summary of Feedback Controls in Cellular Respiration			
Pathway	**Enzyme affected**	**Elevated levels of effector**	**Effect on pathway activity**
glycolysis	hexokinase	glucose-6-phosphate	decrease

Summary of Feedback Controls in Cellular Respiration			
Pathway	**Enzyme affected**	**Elevated levels of effector**	**Effect on pathway activity**
	phosphofructokinase	low-energy charge (ATP, AMP), fructose-6-phosphate via fructose-2,6-bisphosphate	increase
		high-energy charge (ATP, AMP), citrate, acidic pH	decrease
	pyruvate kinase	fructose-1,6-bisphosphate	increase
		high-energy charge (ATP, AMP), alanine	decrease
pyruvate to acetyl CoA conversion	pyruvate dehydrogenase	ADP, pyruvate	increase

Summary of Feedback Controls in Cellular Respiration			
Pathway	**Enzyme affected**	**Elevated levels of effector**	**Effect on pathway activity**
citric acid cycle	isocitrate dehydrogenase	acetyl CoA, ATP, NADH	decrease
		ADP	increase
		ATP, NADH	decrease
	α-ketoglutarate dehydrogenase	Calcium ions, ADP	increase
		ATP, NADH, succinyl CoA	decrease
electron transport chain		ADP	increase
		ATP	decrease

Section Summary

Cellular respiration is controlled by a variety of means. The entry of glucose into a cell is controlled by the transport proteins that aid glucose passage through the cell membrane. Most of the control of the respiration processes is accomplished through the control of specific enzymes in the pathways. This is a type of negative feedback, turning the enzymes off. The

enzymes respond most often to the levels of the available nucleosides ATP, ADP, AMP, NAD⁺, and FAD. Other intermediates of the pathway also affect certain enzymes in the systems.

Review Questions

Exercise:

Problem: The effect of high levels of ADP is to _____.

    a. increase the activity of the enzyme
    b. decrease the activity of the enzyme
    c. have no effect on the activity of the enzyme
    d. slow down the pathway

Solution:

A

Exercise:

Problem:

The control of which enzyme exerts the most control on glycolysis?

    a. hexokinase
    b. phosphofructokinase
    c. glucose-6-phosphatase
    d. aldolase

Solution:

B

Free Response

Exercise:

Problem: How does citrate from the citric acid cycle affect glycolysis?

Solution:

Citrate can inhibit phosphofructokinase by feedback regulation.

Exercise:

Problem:

Why might negative feedback mechanisms be more common than positive feedback mechanisms in living cells?

Solution:

Negative feedback mechanisms actually control a process; it can turn it off, whereas positive feedback accelerates the process, allowing the cell no control over it. Negative feedback naturally maintains homeostasis, whereas positive feedback drives the system away from equilibrium.

Glossary

GLUT protein
    integral membrane protein that transports glucose

Introduction
class="introduction"

Have you ever become separated from a friend while in a crowd? If so, you know the challenge of searching for someone when surrounded by thousands of other people. If you and your friend have cell phones, your chances of finding each other are good. A cell phone's ability to send and receive messages makes it an ideal communication device. (credit: modification of work by Vincent and Bella Productions)

Imagine what life would be like if you and the people around you could not communicate. You would not be able to express your wishes to others, nor could you ask questions to find out more about your environment. Social organization is dependent on communication between the individuals that comprise that society; without communication, society would fall apart.

As with people, it is vital for individual cells to be able to interact with their environment. This is true whether a cell is growing by itself in a pond or is one of many cells that form a larger organism. In order to properly respond to external stimuli, cells have developed complex mechanisms of communication that can receive a message, transfer the information across the plasma membrane, and then produce changes within the cell in response to the message.

In multicellular organisms, cells send and receive chemical messages constantly to coordinate the actions of distant organs, tissues, and cells. The ability to send messages quickly and efficiently enables cells to coordinate and fine-tune their functions.

While the necessity for cellular communication in larger organisms seems obvious, even single-celled organisms communicate with each other. Yeast cells signal each other to aid mating. Some forms of bacteria coordinate their actions in order to form large complexes called biofilms or to organize the production of toxins to remove competing organisms. The ability of cells to communicate through chemical signals originated in single cells and was essential for the evolution of multicellular organisms. The efficient and error-free function of communication systems is vital for all life as we know it.

Signaling Molecules and Cellular Receptors
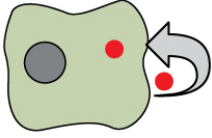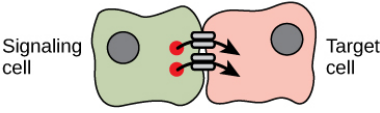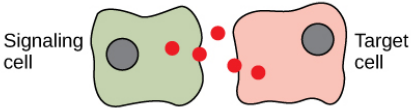By the end of this section, you will be able to:

- Describe four types of signaling found in multicellular organisms
- Compare internal receptors with cell-surface receptors
- Recognize the relationship between a ligand's structure and its mechanism of action

There are two kinds of communication in the world of living cells. Communication between cells is called **intercellular signaling**, and communication within a cell is called **intracellular signaling**. An easy way to remember the distinction is by understanding the Latin origin of the prefixes: inter- means "between" (for example, intersecting lines are those that cross each other) and intra- means "inside" (like intravenous).

Chemical signals are released by **signaling cells** in the form of small, usually volatile or soluble molecules called ligands. A **ligand** is a molecule that binds another specific molecule, in some cases, delivering a signal in the process. Ligands can thus be thought of as signaling molecules. Ligands interact with proteins in **target cells**, which are cells that are affected by chemical signals; these proteins are also called **receptors**. Ligands and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.

Forms of Signaling

There are four categories of chemical signaling found in multicellular organisms: paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions ([link]). The main difference between the different categories of signaling is the distance that the signal travels through the organism to reach the target cell. Not all cells are affected by the same signals.

Forms of Chemical Signaling	
Autocrine	A cell targets itself.

Signaling across gap junctions	A cell targets a cell connected by gap junctions.

Paracrine	A cell targets a nearby cell.

Endocrine	A cell targets a distant cell through the bloodstream.

In chemical signaling, a cell may target itself (autocrine signaling), a cell connected by gap junctions, a nearby cell (paracrine signaling), or a distant cell (endocrine signaling). Paracrine signaling acts on nearby cells, endocrine signaling uses the circulatory system to transport ligands, and autocrine signaling acts on the signaling cell. Signaling via gap junctions involves signaling molecules moving directly between adjacent cells.
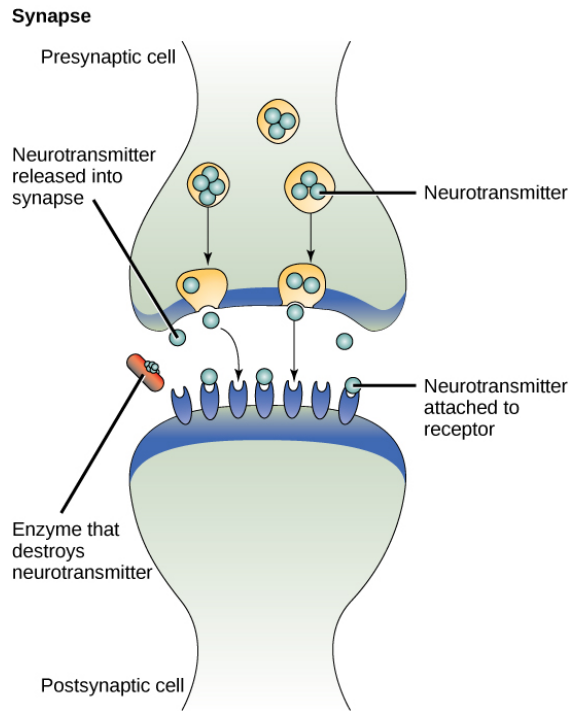
Paracrine Signaling

Signals that act locally between cells that are close together are called **paracrine signals**. Paracrine signals move by diffusion through the

extracellular matrix. These types of signals usually elicit quick responses that last only a short amount of time. In order to keep the response localized, paracrine ligand molecules are normally quickly degraded by enzymes or removed by neighboring cells. Removing the signals will reestablish the concentration gradient for the signal, allowing them to quickly diffuse through the intracellular space if released again.

One example of paracrine signaling is the transfer of signals across synapses between nerve cells. A nerve cell consists of a cell body, several short, branched extensions called dendrites that receive stimuli, and a long extension called an axon, which transmits signals to other nerve cells or muscle cells. The junction between nerve cells where signal transmission occurs is called a synapse. A **synaptic signal** is a chemical signal that travels between nerve cells. Signals within the nerve cells are propagated by fast-moving electrical impulses. When these impulses reach the end of the axon, the signal continues on to a dendrite of the next cell by the release of chemical ligands called **neurotransmitters** by the presynaptic cell (the cell emitting the signal). The neurotransmitters are transported across the very small distances between nerve cells, which are called **chemical synapses** ([link]). The small distance between nerve cells allows the signal to travel quickly; this enables an immediate response, such as, Take your hand off the stove!

When the neurotransmitter binds the receptor on the surface of the postsynaptic cell, the electrochemical potential of the target cell changes, and the next electrical impulse is launched. The neurotransmitters that are released into the chemical synapse are degraded quickly or get reabsorbed by the presynaptic cell so that the recipient nerve cell can recover quickly and be prepared to respond rapidly to the next synaptic signal.

Synapse

Presynaptic cell

Neurotransmitter released into synapse

Neurotransmitter

Neurotransmitter attached to receptor

Enzyme that destroys neurotransmitter

Postsynaptic cell

The distance between the presynaptic cell and the postsynaptic cell—called the synaptic gap—is very small and allows for rapid diffusion of the neurotransmitter. Enzymes in the synapatic cleft degrade some types of neurotransmitters to terminate the signal.

Endocrine Signaling

Signals from distant cells are called **endocrine signals**, and they originate from **endocrine cells**. (In the body, many endocrine cells are located in endocrine glands, such as the thyroid gland, the hypothalamus, and the pituitary gland.) These types of signals usually produce a slower response

but have a longer-lasting effect. The ligands released in endocrine signaling are called hormones, signaling molecules that are produced in one part of the body but affect other body regions some distance away.

Hormones travel the large distances between endocrine cells and their target cells via the bloodstream, which is a relatively slow way to move throughout the body. Because of their form of transport, hormones get diluted and are present in low concentrations when they act on their target cells. This is different from paracrine signaling, in which local concentrations of ligands can be very high.

Autocrine Signaling

Autocrine signals are produced by signaling cells that can also bind to the ligand that is released. This means the signaling cell and the target cell can be the same or a similar cell (the prefix *auto-* means self, a reminder that the signaling cell sends a signal to itself). This type of signaling often occurs during the early development of an organism to ensure that cells develop into the correct tissues and take on the proper function. Autocrine signaling also regulates pain sensation and inflammatory responses. Further, if a cell is infected with a virus, the cell can signal itself to undergo programmed cell death, killing the virus in the process. In some cases, neighboring cells of the same type are also influenced by the released ligand. In embryological development, this process of stimulating a group of neighboring cells may help to direct the differentiation of identical cells into the same cell type, thus ensuring the proper developmental outcome.

Direct Signaling Across Gap Junctions

Gap junctions in animals and plasmodesmata in plants are connections between the plasma membranes of neighboring cells. These water-filled channels allow small signaling molecules, called **intracellular mediators**, to diffuse between the two cells. Small molecules, such as calcium ions (Ca^{2+}), are able to move between cells, but large molecules like proteins

and DNA cannot fit through the channels. The specificity of the channels ensures that the cells remain independent but can quickly and easily transmit signals. The transfer of signaling molecules communicates the current state of the cell that is directly next to the target cell; this allows a group of cells to coordinate their response to a signal that only one of them may have received. In plants, plasmodesmata are ubiquitous, making the entire plant into a giant, communication network.

Types of Receptors

Receptors are protein molecules in the target cell or on its surface that bind ligand. There are two types of receptors, internal receptors and cell-surface receptors.

Internal receptors

Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane. Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis (transcription) to mediate gene expression. Gene expression is the cellular process of transforming the information in a cell's DNA into a sequence of amino acids, which ultimately forms a protein. When the ligand binds to the internal receptor, a conformational change is triggered that exposes a DNA-binding site on the protein. The ligand-receptor complex moves into the nucleus, then binds to specific regulatory regions of the chromosomal DNA and promotes the initiation of transcription ([link]). Transcription is the process of copying the information in a cells DNA into a special form of RNA called messenger RNA (mRNA); the cell uses information in the mRNA (which moves out into the cytoplasm and associates with ribosomes) to link specific amino acids in the correct order, producing a protein. Internal receptors can directly influence gene expression without having to pass the signal on to other receptors or messengers.
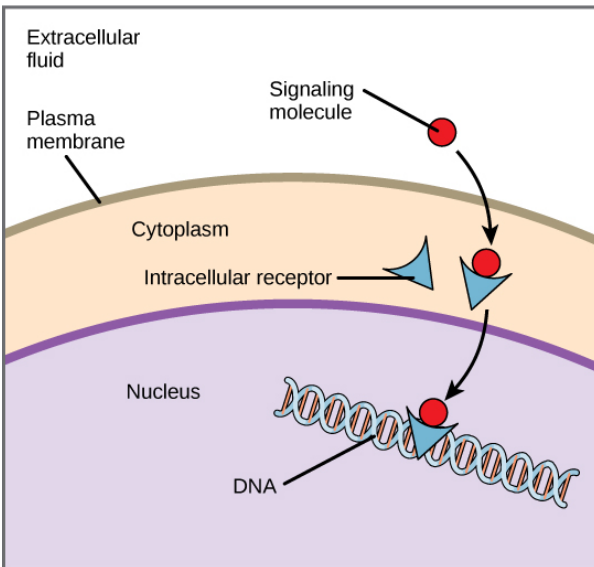
Hydrophobic signaling molecules typically diffuse across the plasma membrane and interact with intracellular receptors in the cytoplasm. Many intracellular receptors are transcription factors that interact with DNA in the nucleus and regulate gene expression.

Cell-Surface Receptors

Cell-surface receptors, also known as transmembrane receptors, are cell surface, membrane-anchored (integral) proteins that bind to external ligand molecules. This type of receptor spans the plasma membrane and performs signal transduction, in which an extracellular signal is converted into an intercellular signal. Ligands that interact with cell-surface receptors do not have to enter the cell that they affect. Cell-surface receptors are also called

cell-specific proteins or markers because they are specific to individual cell types.

Because cell-surface receptor proteins are fundamental to normal cell functioning, it should come as no surprise that a malfunction in any one of these proteins could have severe consequences. Errors in the protein structures of certain receptor molecules have been shown to play a role in hypertension (high blood pressure), asthma, heart disease, and cancer.

Each cell-surface receptor has three main components: an external ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular domain inside the cell. The ligand-binding domain is also called the **extracellular domain**. The size and extent of each of these domains vary widely, depending on the type of receptor.

Note:
Evolution Connection
How Viruses Recognize a Host
Unlike living cells, many viruses do not have a plasma membrane or any of the structures necessary to sustain life. Some viruses are simply composed of an inert protein shell containing DNA or RNA. To reproduce, viruses must invade a living cell, which serves as a host, and then take over the hosts cellular apparatus. But how does a virus recognize its host?
Viruses often bind to cell-surface receptors on the host cell. For example, the virus that causes human influenza (flu) binds specifically to receptors on membranes of cells of the respiratory system. Chemical differences in the cell-surface receptors among hosts mean that a virus that infects a specific species (for example, humans) cannot infect another species (for example, chickens).
However, viruses have very small amounts of DNA or RNA compared to humans, and, as a result, viral reproduction can occur rapidly. Viral reproduction invariably produces errors that can lead to changes in newly produced viruses; these changes mean that the viral proteins that interact with cell-surface receptors may evolve in such a way that they can bind to receptors in a new host. Such changes happen randomly and quite often in the reproductive cycle of a virus, but the changes only matter if a virus

with new binding properties comes into contact with a suitable host. In the case of influenza, this situation can occur in settings where animals and people are in close contact, such as poultry and swine farms.^[footnote] Once a virus jumps to a new host, it can spread quickly. Scientists watch newly appearing viruses (called emerging viruses) closely in the hope that such monitoring can reduce the likelihood of global viral epidemics.

A. B. Sigalov, The School of Nature. IV. Learning from Viruses, *Self/Nonself* 1, no. 4 (2010): 282-298. Y. Cao, X. Koh, L. Dong, X. Du, A. Wu, X. Ding, H. Deng, Y. Shu, J. Chen, T. Jiang, Rapid Estimation of Binding Activity of Influenza Virus Hemagglutinin to Human and Avian Receptors, *PLoS One* 6, no. 4 (2011): e18664.

Cell-surface receptors are involved in most of the signaling in multicellular organisms. There are three general categories of cell-surface receptors: ion channel-linked receptors, G-protein-linked receptors, and enzyme-linked receptors.

Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell-surface receptor has an extensive membrane-spanning region. In order to interact with the phospholipid fatty acid tails that form the center of the plasma membrane, many of the amino acids in the membrane-spanning region are hydrophobic in nature. Conversely, the amino acids that line the inside of the channel are hydrophilic to allow for the passage of water or ions. When a ligand binds to the extracellular region of the channel, there is a conformational change in the proteins structure that allows ions such as sodium, calcium, magnesium, and hydrogen to pass through ([link]).
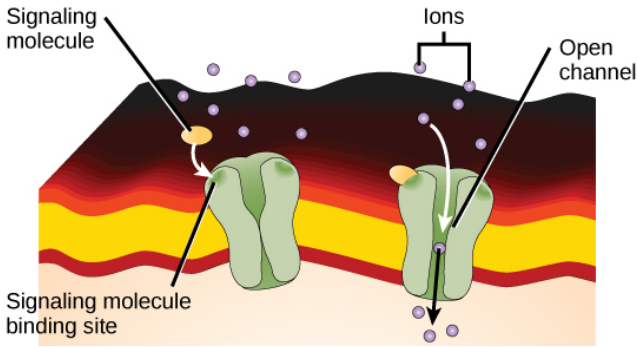
Gated ion channels form a pore through the plasma membrane that opens when the signaling molecule binds. The open pore then allows ions to flow into or out of the cell.

G-protein-linked receptors bind a ligand and activate a membrane protein called a G-protein. The activated G-protein then interacts with either an ion channel or an enzyme in the membrane ([link]). All G-protein-linked receptors have seven transmembrane domains, but each receptor has its own specific extracellular domain and G-protein-binding site.

Cell signaling using G-protein-linked receptors occurs as a cyclic series of events. Before the ligand binds, the inactive G-protein can bind to a newly revealed site on the receptor specific for its binding. Once the ligand binds to the receptor, the resultant shape change activates the G-protein, which releases GDP and picks up GTP. The subunits of the G-protein then split into the α subunit and the $\beta\gamma$ subunit. One or both of these G-protein fragments may be able to activate other proteins as a result. After a while, the GTP on the active α subunit of the G-protein is hydrolyzed to GDP and the $\beta\gamma$ subunit is deactivated. The subunits reassociate to form the inactive G-protein and the cycle begins anew.
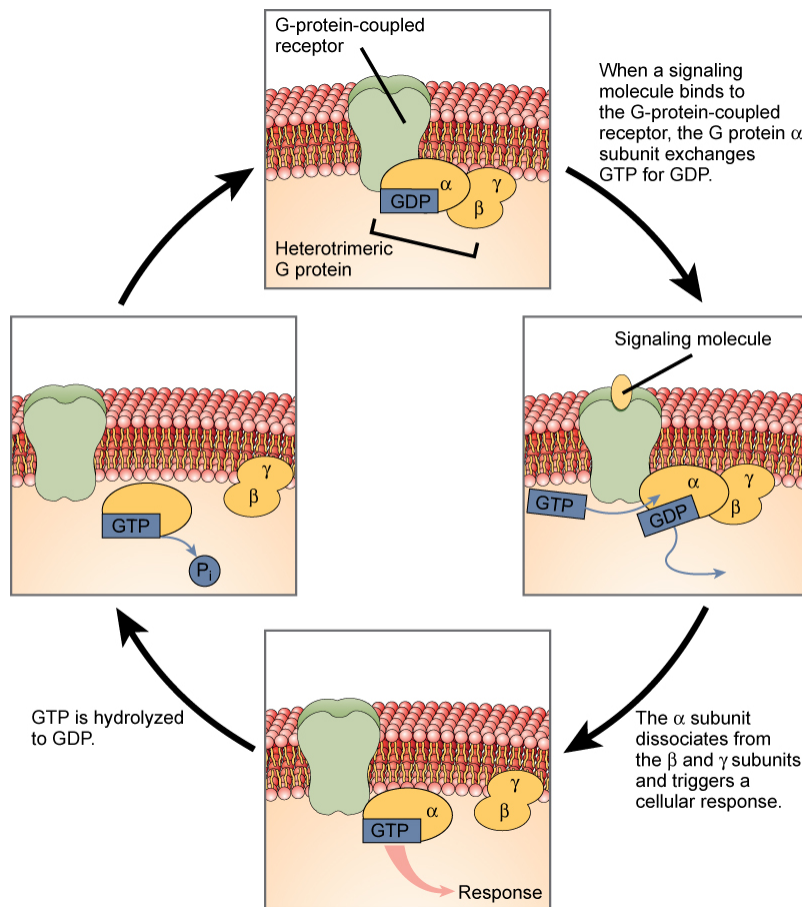
Heterotrimeric G proteins have three subunits: α, β, and γ. When a signaling molecule binds to a G-protein-coupled receptor in the plasma membrane, a GDP molecule associated with the α subunit is exchanged for GTP. The β and γ subunits dissociate from the α subunit, and a cellular response is triggered either by the α subunit or the dissociated $\beta\gamma$ pair. Hydrolysis of GTP to GDP terminates the signal.

G-protein-linked receptors have been extensively studied and much has been learned about their roles in maintaining health. Bacteria that are pathogenic to humans can release poisons that interrupt specific G-protein-

linked receptor function, leading to illnesses such as pertussis, botulism, and cholera. In cholera ([link]), for example, the water-borne bacterium *Vibrio cholerae* produces a toxin, choleragen, that binds to cells lining the small intestine. The toxin then enters these intestinal cells, where it modifies a G-protein that controls the opening of a chloride channel and causes it to remain continuously active, resulting in large losses of fluids from the body and potentially fatal dehydration as a result.
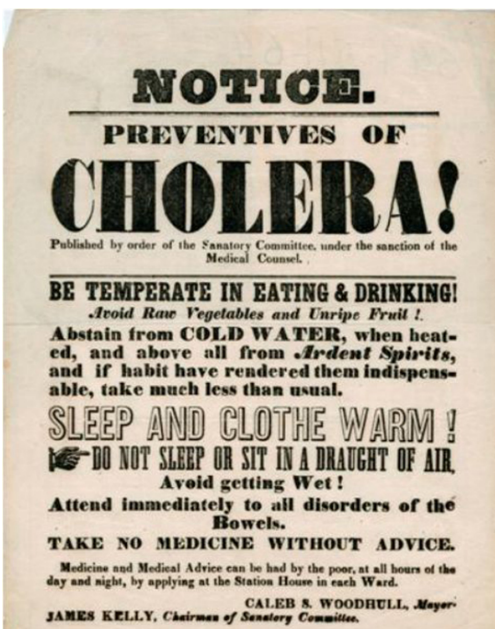

Transmitted primarily through contaminated drinking water, cholera is a major cause of death in the developing world and in areas where natural disasters interrupt the availability of clean water. The cholera bacterium, *Vibrio cholerae,* creates a toxin that modifies G-protein-mediated cell signaling

pathways in the intestines. Modern sanitation eliminates the threat of cholera outbreaks, such as the one that swept through New York City in 1866. This poster from that era shows how, at that time, the way that the disease was transmitted was not understood. (credit: New York City Sanitary Commission)

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor itself is an enzyme. Other enzyme-linked receptors have a small intracellular domain that interacts directly with an enzyme. The enzyme-linked receptors normally have large extracellular and intracellular domains, but the membrane-spanning region consists of a single alpha-helical region of the peptide strand. When a ligand binds to the extracellular domain, a signal is transferred through the membrane, activating the enzyme. Activation of the enzyme sets off a chain of events within the cell that eventually leads to a response. One example of this type of enzyme-linked receptor is the tyrosine kinase receptor ([link]). A kinase is an enzyme that transfers phosphate groups from ATP to another protein. The tyrosine kinase receptor transfers phosphate groups to tyrosine molecules (tyrosine residues). First, signaling molecules bind to the extracellular domain of two nearby tyrosine kinase receptors. The two neighboring receptors then bond together, or dimerize. Phosphates are then added to tyrosine residues on the intracellular domain of the receptors (phosphorylation). The phosphorylated residues can then transmit the signal to the next messenger within the cytoplasm.

Plasma membrane

Receptor tyrosine kinase

Cytoplasm

When signaling molecules bind the receptors, the receptors dimerize.

Signaling molecule

Tyrosine residues

Tyrosine residues on the intracellular domain are phosphorylated, triggering a downstream cellular response.

Phosphorylated tyrosine residues

Cellular response
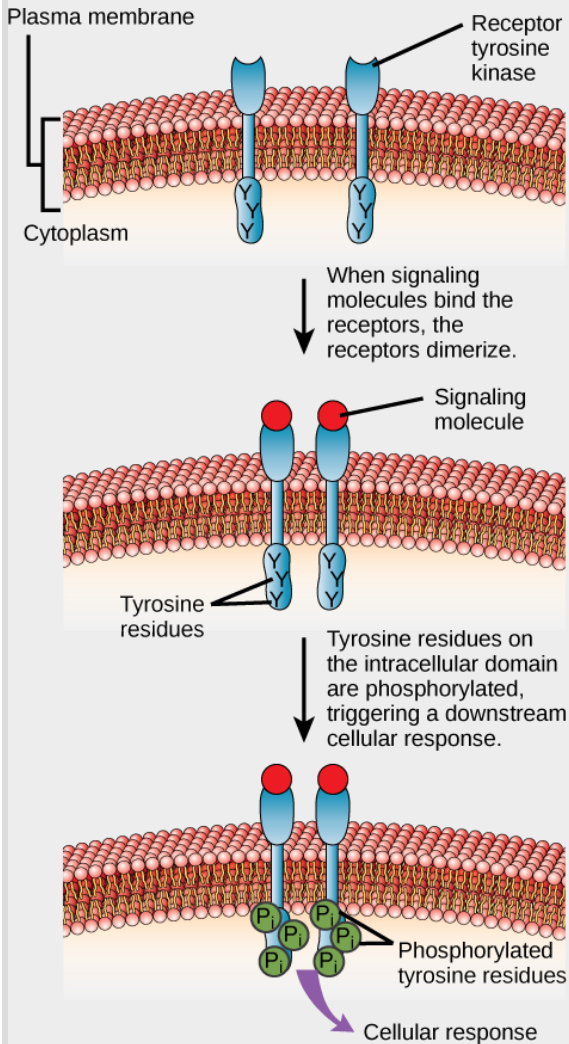
A receptor tyrosine kinase is an enzyme-linked receptor with a single transmembrane region, and extracellular and intracellular domains. Binding of a signaling molecule to the extracellular domain causes the receptor to dimerize. Tyrosine residues on the intracellular domain are then autophosphorylated,

triggering a downstream cellular response. The signal is terminated by a phosphatase that removes the phosphates from the phosphotyrosine residues.

HER2 is a receptor tyrosine kinase. In 30 percent of human breast cancers, HER2 is permanently activated, resulting in unregulated cell division. Lapatinib, a drug used to treat breast cancer, inhibits HER2 receptor tyrosine kinase autophosphorylation (the process by which the receptor adds phosphates onto itself), thus reducing tumor growth by 50 percent. Besides autophosphorylation, which of the following steps would be inhibited by Lapatinib?

a. Signaling molecule binding, dimerization, and the downstream cellular response
b. Dimerization, and the downstream cellular response
c. The downstream cellular response
d. Phosphatase activity, dimerization, and the downsteam cellular response

Signaling Molecules

Produced by signaling cells and the subsequent binding to receptors in target cells, ligands act as chemical signals that travel to the target cells to coordinate responses. The types of molecules that serve as ligands are incredibly varied and range from small proteins to small ions like calcium (Ca^{2+}).

Small Hydrophobic Ligands

Small hydrophobic ligands can directly diffuse through the plasma membrane and interact with internal receptors. Important members of this class of ligands are the steroid hormones. Steroids are lipids that have a hydrocarbon skeleton with four fused rings; different steroids have different functional groups attached to the carbon skeleton. Steroid hormones include the female sex hormone, estradiol, which is a type of estrogen; the male sex hormone, testosterone; and cholesterol, which is an important structural component of biological membranes and a precursor of steriod hormones ([link]). Other hydrophobic hormones include thyroid hormones and vitamin D. In order to be soluble in blood, hydrophobic ligands must bind to carrier proteins while they are being transported through the bloodstream.
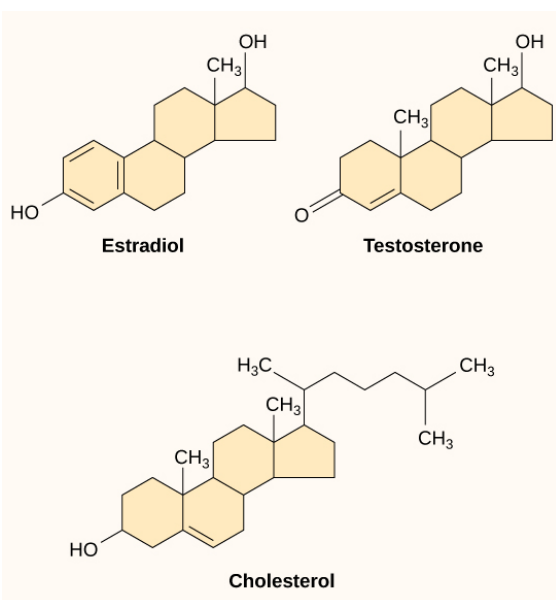
Steroid hormones have similar chemical structures to their precursor, cholesterol. Because these molecules are small and hydrophobic, they can diffuse directly across the plasma membrane into the cell, where they interact with internal receptors.

Water-Soluble Ligands

Water-soluble ligands are polar and therefore cannot pass through the plasma membrane unaided; sometimes, they are too large to pass through the membrane at all. Instead, most water-soluble ligands bind to the extracellular domain of cell-surface receptors. This group of ligands is quite diverse and includes small molecules, peptides, and proteins.

Other Ligands

Nitric oxide (NO) is a gas that also acts as a ligand. It is able to diffuse directly across the plasma membrane, and one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue. NO has a very short half-life and therefore only functions over short distances. Nitroglycerin, a treatment for heart disease, acts by triggering the release of NO, which causes blood vessels to dilate (expand), thus restoring blood flow to the heart. NO has become better known recently because the pathway that it affects is targeted by prescription medications for erectile dysfunction, such as Viagra (erection involves dilated blood vessels).

Section Summary

Cells communicate by both inter- and intracellular signaling. Signaling cells secrete ligands that bind to target cells and initiate a chain of events within the target cell. The four categories of signaling in multicellular organisms are paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions. Paracrine signaling takes place over short distances. Endocrine signals are carried long distances through the bloodstream by hormones, and autocrine signals are received by the same cell that sent the signal or other nearby cells of the same kind. Gap junctions allow small molecules, including signaling molecules, to flow between neighboring cells.

Internal receptors are found in the cell cytoplasm. Here, they bind ligand molecules that cross the plasma membrane; these receptor-ligand complexes move to the nucleus and interact directly with cellular DNA. Cell-surface receptors transmit a signal from outside the cell to the cytoplasm. Ion channel-linked receptors, when bound to their ligands, form a pore through the plasma membrane through which certain ions can pass. G-protein-linked receptors interact with a G-protein on the cytoplasmic side of the plasma membrane, promoting the exchange of bound GDP for GTP and interacting with other enzymes or ion channels to transmit a signal. Enzyme-linked receptors transmit a signal from outside the cell to an intracellular domain of a membrane-bound enzyme. Ligand binding causes activation of the enzyme. Small hydrophobic ligands (like steroids) are able to penetrate the plasma membrane and bind to internal receptors. Water-soluble hydrophilic ligands are unable to pass through the membrane; instead, they bind to cell-surface receptors, which transmit the signal to the inside of the cell.

Art Connections

Exercise:

Problem:

[link] HER2 is a receptor tyrosine kinase. In 30 percent of human breast cancers, HER2 is permanently activated, resulting in unregulated cell division. Lapatinib, a drug used to treat breast cancer, inhibits HER2 receptor tyrosine kinase autophosphorylation (the process by which the receptor adds phosphates onto itself), thus reducing tumor growth by 50 percent. Besides autophosphorylation, which of the following steps would be inhibited by Lapatinib?

a. Signaling molecule binding, dimerization, and the downstream cellular response.
b. Dimerization, and the downstream cellular response.
c. The downstream cellular response.
d. Phosphatase activity, dimerization, and the downsteam cellular response.

Solution:

C. The downstream cellular response would be inhibited.

Review Questions

Exercise:

Problem:

What property prevents the ligands of cell-surface receptors from entering the cell?

- a. The molecules bind to the extracellular domain.
- b. The molecules are hydrophilic and cannot penetrate the hydrophobic interior of the plasma membrane.
- c. The molecules are attached to transport proteins that deliver them through the bloodstream to target cells.
- d. The ligands are able to penetrate the membrane and directly influence gene expression upon receptor binding.

Solution:

B

Exercise:

Problem:

The secretion of hormones by the pituitary gland is an example of _____.

- a. autocrine signaling
- b. paracrine signaling
- c. endocrine signaling
- d. direct signaling across gap junctions

Solution:

C

Exercise:

Problem:

Why are ion channels necessary to transport ions into or out of a cell?

    a. Ions are too large to diffuse through the membrane.
    b. Ions are charged particles and cannot diffuse through the hydrophobic interior of the membrane.
    c. Ions do not need ion channels to move through the membrane.
    d. Ions bind to carrier proteins in the bloodstream, which must be removed before transport into the cell.

Solution:

B

Exercise:

Problem:

Endocrine signals are transmitted more slowly than paracrine signals because _____.

    a. the ligands are transported through the bloodstream and travel greater distances
    b. the target and signaling cells are close together
    c. the ligands are degraded rapidly
    d. the ligands don't bind to carrier proteins during transport

Solution:

A

Free Response

Exercise:

Problem:

What is the difference between intracellular signaling and intercellular signaling?

Solution:

Intracellular signaling occurs within a cell, and intercellular signaling occurs between cells.

Exercise:

Problem:

How are the effects of paracrine signaling limited to an area near the signaling cells?

Solution:

The secreted ligands are quickly removed by degradation or reabsorption into the cell so that they cannot travel far.

Exercise:

Problem:

What are the differences between internal receptors and cell-surface receptors?

Solution:

Internal receptors are located inside the cell, and their ligands enter the cell to bind the receptor. The complex formed by the internal receptor and the ligand then enters the nucleus and directly affects protein production by binding to the chromosomal DNA and initiating the making of mRNA that codes for proteins. Cell-surface receptors, however, are embedded in the plasma membrane, and their ligands do

not enter the cell. Binding of the ligand to the cell-surface receptor initiates a cell signaling cascade and does not directly influence the making of proteins; however, it may involve the activation of intracellular proteins.

Exercise:

Problem:

Cells grown in the laboratory are mixed with a dye molecule that is unable to pass through the plasma membrane. If a ligand is added to the cells, observations show that the dye enters the cells. What type of receptor did the ligand bind to on the cell surface?

Solution:

An ion channel receptor opened up a pore in the membrane, which allowed the ionic dye to move into the cell.

Glossary

autocrine signal
   signal that is sent and received by the same or similar nearby cells

cell-surface receptor
   cell-surface protein that transmits a signal from the exterior of the cell to the interior, even though the ligand does not enter the cell

chemical synapse
   small space between axon terminals and dendrites of nerve cells where neurotransmitters function

endocrine cell
   cell that releases ligands involved in endocrine signaling (hormones)

endocrine signal
   long-distance signal that is delivered by ligands (hormones) traveling through an organisms circulatory system from the signaling cell to the

target cell

enzyme-linked receptor
cell-surface receptor with intracellular domains that are associated with membrane-bound enzymes

extracellular domain
region of a cell-surface receptor that is located on the cell surface

G-protein-linked receptor
cell-surface receptor that activates membrane-bound G-proteins to transmit a signal from the receptor to nearby membrane components

intercellular signaling
communication between cells

internal receptor
(also, intracellular receptor) receptor protein that is located in the cytosol of a cell and binds to ligands that pass through the plasma membrane

intracellular mediator
(also, second messenger) small molecule that transmits signals within a cell

intracellular signaling
communication within cells

ion channel-linked receptor
cell-surface receptor that forms a plasma membrane channel, which opens when a ligand binds to the extracellular domain (ligand-gated channels)

ligand
molecule produced by a signaling cell that binds with a specific receptor, delivering a signal in the process

neurotransmitter

chemical ligand that carries a signal from one nerve cell to the next

paracrine signal
signal between nearby cells that is delivered by ligands traveling in the liquid medium in the space between the cells

receptor
protein in or on a target cell that bind to ligands

signaling cell
cell that releases signal molecules that allow communication with another cell

synaptic signal
chemical signal (neurotransmitter) that travels between nerve cells

target cell
cell that has a receptor for a signal or ligand from a signaling cell

Propagation of the Signal
By the end of this section, you will be able to:

- Explain how the binding of a ligand initiates signal transduction throughout a cell
- Recognize the role of phosphorylation in the transmission of intracellular signals
- Evaluate the role of second messengers in signal transmission

Once a ligand binds to a receptor, the signal is transmitted through the membrane and into the cytoplasm. Continuation of a signal in this manner is called **signal transduction**. Signal transduction only occurs with cell-surface receptors because internal receptors are able to interact directly with DNA in the nucleus to initiate protein synthesis.
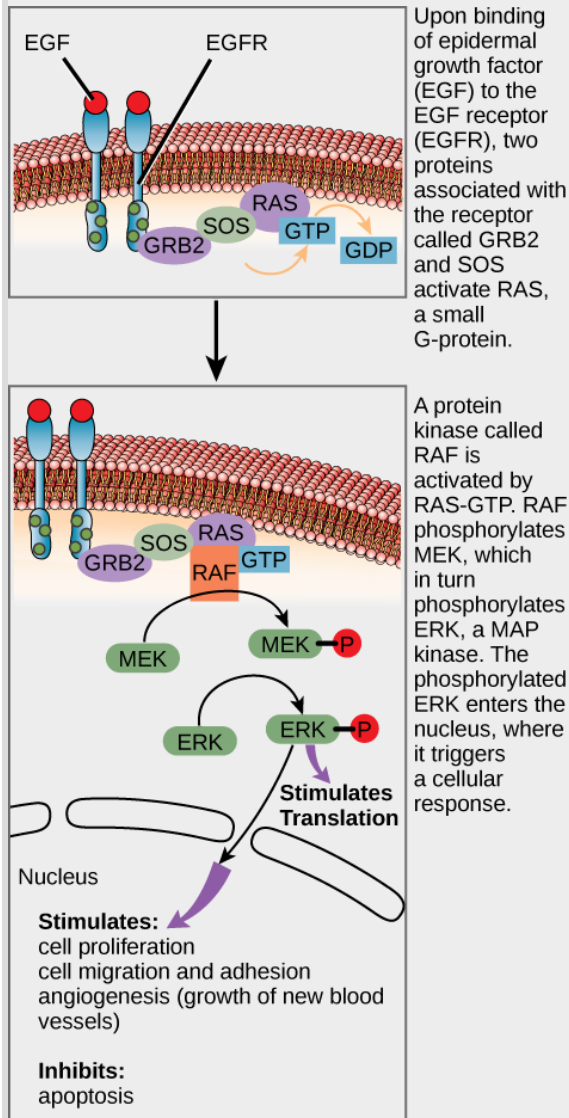
When a ligand binds to its receptor, conformational changes occur that affect the receptor's intracellular domain. Conformational changes of the extracellular domain upon ligand binding can propagate through the membrane region of the receptor and lead to activation of the intracellular domain or its associated proteins. In some cases, binding of the ligand causes **dimerization** of the receptor, which means that two receptors bind to each other to form a stable complex called a dimer. A **dimer** is a chemical compound formed when two molecules (often identical) join together. The binding of the receptors in this manner enables their intracellular domains to come into close contact and activate each other.

Binding Initiates a Signaling Pathway

After the ligand binds to the cell-surface receptor, the activation of the receptor's intracellular components sets off a chain of events that is called a **signaling pathway** or a signaling cascade. In a signaling pathway, second messengers, enzymes, and activated proteins interact with specific proteins, which are in turn activated in a chain reaction that eventually leads to a change in the cell's environment ([link]). The events in the cascade occur in a series, much like a current flows in a river. Interactions that occur before a certain point are defined as upstream events, and events after that point are called downstream events.

Note:

Art Connection

Upon binding of epidermal growth factor (EGF) to the EGF receptor (EGFR), two proteins associated with the receptor called GRB2 and SOS activate RAS, a small G-protein.

A protein kinase called RAF is activated by RAS-GTP. RAF phosphorylates MEK, which in turn phosphorylates ERK, a MAP kinase. The phosphorylated ERK enters the nucleus, where it triggers a cellular response.

The epidermal growth factor (EGF) receptor (EGFR) is a receptor tyrosine kinase involved in the regulation of cell growth, wound healing, and tissue repair. When EGF binds to the EGFR, a cascade of downstream events causes the cell to grow and divide. If EGFR is activated at

In certain cancers, the GTPase activity of the RAS G-protein is inhibited. This means that the RAS protein can no longer hydrolyze GTP into GDP. What effect would this have on downstream cellular events?

Signaling pathways can get very complicated very quickly because most cellular proteins can affect different downstream events, depending on the conditions within the cell. A single pathway can branch off toward different endpoints based on the interplay between two or more signaling pathways, and the same ligands are often used to initiate different signals in different cell types. This variation in response is due to differences in protein expression in different cell types. Another complicating element is **signal integration** of the pathways, in which signals from two or more different cell-surface receptors merge to activate the same response in the cell. This process can ensure that multiple external requirements are met before a cell commits to a specific response.

The effects of extracellular signals can also be amplified by enzymatic cascades. At the initiation of the signal, a single ligand binds to a single receptor. However, activation of a receptor-linked enzyme can activate many copies of a component of the signaling cascade, which amplifies the signal.

Methods of Intracellular Signaling

The induction of a signaling pathway depends on the modification of a cellular component by an enzyme. There are numerous enzymatic modifications that can occur, and they are recognized in turn by the next component downstream. The following are some of the more common events in intracellular signaling.
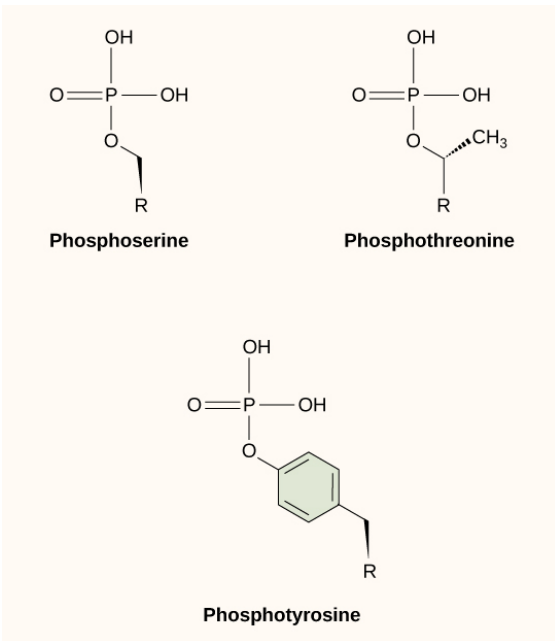
Phosphorylation

One of the most common chemical modifications that occurs in signaling pathways is the addition of a phosphate group (PO_4^{-3}) to a molecule such as a protein in a process called phosphorylation. The phosphate can be added to a nucleotide such as GMP to form GDP or GTP. Phosphates are also often added to serine, threonine, and tyrosine residues of proteins, where they replace the hydroxyl group of the amino acid ([[link]](#)). The transfer of the phosphate is catalyzed by an enzyme called a **kinase**. Various kinases are named for the substrate they phosphorylate. Phosphorylation of serine and threonine residues often activates enzymes. Phosphorylation of tyrosine residues can either affect the activity of an enzyme or create a binding site that interacts with downstream components in the signaling cascade. Phosphorylation may activate or inactivate enzymes, and the reversal of phosphorylation, dephosphorylation by a phosphatase, will reverse the effect.

In protein phosphorylation, a phosphate group (PO_4^{-3}) is added to residues of the amino acids serine, threonine, and tyrosine.

Second Messengers

Second messengers are small molecules that propagate a signal after it has been initiated by the binding of the signaling molecule to the receptor. These molecules help to spread a signal through the cytoplasm by altering the behavior of certain cellular proteins.

Calcium ion is a widely used second messenger. The free concentration of calcium ions (Ca^{2+}) within a cell is very low because ion pumps in the plasma membrane continuously use adenosine-5'-triphosphate (ATP) to remove it. For signaling purposes, Ca^{2+} is stored in cytoplasmic vesicles, such as the endoplasmic reticulum, or accessed from outside the cell. When signaling occurs, ligand-gated calcium ion channels allow the higher levels

of Ca^{2+} that are present outside the cell (or in intracellular storage compartments) to flow into the cytoplasm, which raises the concentration of cytoplasmic Ca^{2+}. The response to the increase in Ca^{2+} varies, depending on the cell type involved. For example, in the β-cells of the pancreas, Ca^{2+} signaling leads to the release of insulin, and in muscle cells, an increase in Ca^{2+} leads to muscle contractions.

Another second messenger utilized in many different cell types is **cyclic AMP (cAMP)**. Cyclic AMP is synthesized by the enzyme adenylyl cyclase from ATP ([link]). The main role of cAMP in cells is to bind to and activate an enzyme called **cAMP-dependent kinase (A-kinase)**. A-kinase regulates many vital metabolic pathways: It phosphorylates serine and threonine residues of its target proteins, activating them in the process. A-kinase is found in many different types of cells, and the target proteins in each kind of cell are different. Differences give rise to the variation of the responses to cAMP in different cells.
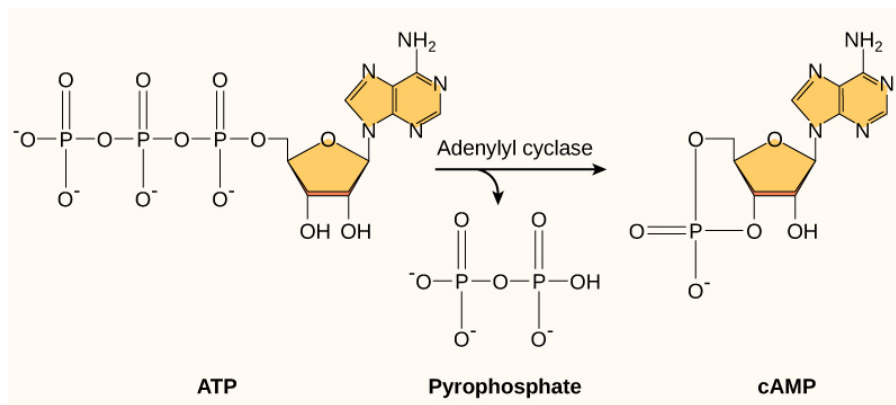
This diagram shows the mechanism for the formation of cyclic AMP (cAMP). cAMP serves as a second messenger to activate or inactivate proteins within the cell. Termination of the signal occurs when an enzyme called phosphodiesterase converts cAMP into AMP.

Present in small concentrations in the plasma membrane, **inositol phospholipids** are lipids that can also be converted into second messengers. Because these molecules are membrane components, they are located near membrane-bound receptors and can easily interact with them. Phosphatidylinositol (PI) is the main phospholipid that plays a role in cellular signaling. Enzymes known as kinases phosphorylate PI to form PI-phosphate (PIP) and PI-bisphosphate (PIP$_2$).

The enzyme phospholipase C cleaves PIP$_2$ to form **diacylglycerol (DAG)** and **inositol triphosphate (IP$_3$)** ([link]). These products of the cleavage of PIP$_2$ serve as second messengers. Diacylglycerol (DAG) remains in the plasma membrane and activates protein kinase C (PKC), which then phosphorylates serine and threonine residues in its target proteins. IP$_3$ diffuses into the cytoplasm and binds to ligand-gated calcium channels in the endoplasmic reticulum to release Ca^{2+} that continues the signal cascade.
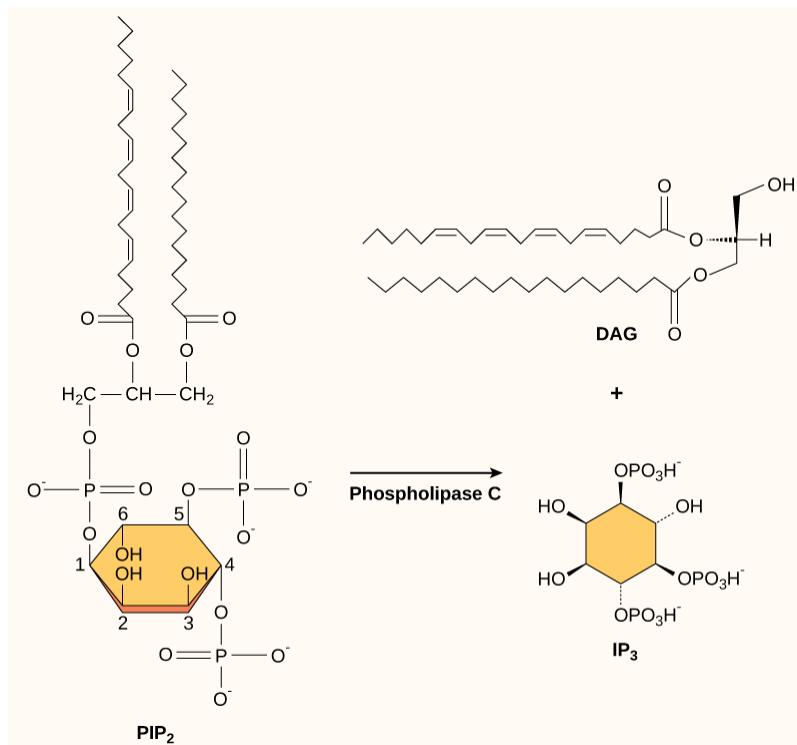
The enzyme phospholipase C breaks down PIP$_2$ into IP$_3$ and DAG, both of which serve

as second messengers.

Section Summary

Ligand binding to the receptor allows for signal transduction through the cell. The chain of events that conveys the signal through the cell is called a signaling pathway or cascade. Signaling pathways are often very complex because of the interplay between different proteins. A major component of cell signaling cascades is the phosphorylation of molecules by enzymes known as kinases. Phosphorylation adds a phosphate group to serine, threonine, and tyrosine residues in a protein, changing their shapes, and activating or inactivating the protein. Small molecules like nucleotides can also be phosphorylated. Second messengers are small, non-protein molecules that are used to transmit a signal within a cell. Some examples of second messengers are calcium ions (Ca^{2+}), cyclic AMP (cAMP), diacylglycerol (DAG), and inositol triphosphate (IP_3).

Art Connections

Exercise:

Problem:

[link] In certain cancers, the GTPase activity of the RAS G-protein is inhibited. This means that the RAS protein can no longer hydrolyze GTP into GDP. What effect would this have on downstream cellular events?

Solution:

[link] ERK would become permanently activated, resulting in cell proliferation, migration, adhesion, and the growth of new blood vessels. Apoptosis would be inhibited.

Review Questions

Exercise:

Problem: Where do DAG and IP_3 originate?

    a. They are formed by phosphorylation of cAMP.
    b. They are ligands expressed by signaling cells.
    c. They are hormones that diffuse through the plasma membrane to stimulate protein production.
    d. They are the cleavage products of the inositol phospholipid, PIP_2.

Solution:

D

Exercise:

Problem:

What property enables the residues of the amino acids serine, threonine, and tyrosine to be phosphorylated?

    a. They are polar.
    b. They are non-polar.
    c. They contain a hydroxyl group.
    d. They occur more frequently in the amino acid sequence of signaling proteins.

Solution:

C

Free Response

Exercise:

Problem:

The same second messengers are used in many different cells, but the response to second messengers is different in each cell. How is this possible?

Solution:

Different cells produce different proteins, including cell-surface receptors and signaling pathway components. Therefore, they respond to different ligands, and the second messengers activate different pathways. Signal integration can also change the end result of signaling.

Exercise:

Problem:

What would happen if the intracellular domain of a cell-surface receptor was switched with the domain from another receptor?

Solution:

The binding of the ligand to the extracellular domain would activate the pathway normally activated by the receptor donating the intracellular domain.

Glossary

cyclic AMP (cAMP)
    second messenger that is derived from ATP

cyclic AMP-dependent kinase
    (also, protein kinase A, or PKA) kinase that is activated by binding to cAMP

diacylglycerol (DAG)

cleavage product of PIP_2 that is used for signaling within the plasma
membrane

dimer
chemical compound formed when two molecules join together

dimerization
(of receptor proteins) interaction of two receptor proteins to form a
functional complex called a dimer

inositol phospholipid
lipid present at small concentrations in the plasma membrane that is
converted into a second messenger; it has inositol (a carbohydrate) as
its hydrophilic head group

inositol triphosphate (IP_3)
cleavage product of PIP_2 that is used for signaling within the cell

kinase
enzyme that catalyzes the transfer of a phosphate group from ATP to
another molecule

second messenger
small, non-protein molecule that propagates a signal within the cell
after activation of a receptor causes its release

signal integration
interaction of signals from two or more different cell-surface receptors
that merge to activate the same response in the cell

signal transduction
propagation of the signal through the cytoplasm (and sometimes also
the nucleus) of the cell

signaling pathway
(also signaling cascade) chain of events that occurs in the cytoplasm of
the cell to propagate the signal from the plasma membrane to produce
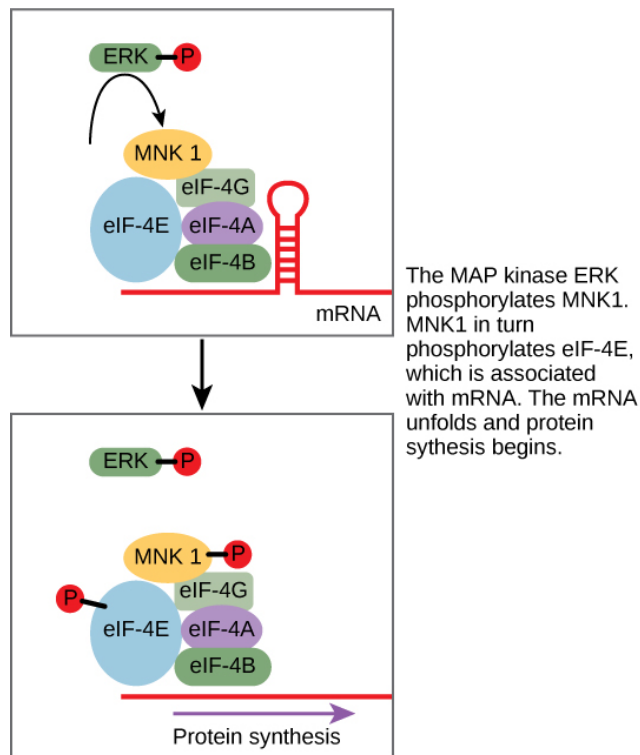a response

Response to the Signal
By the end of this section, you will be able to:

- Describe how signaling pathways direct protein expression, cellular metabolism, and cell growth
- Identify the function of PKC in signal transduction pathways
- Recognize the role of apoptosis in the development and maintenance of a healthy organism

Inside the cell, ligands bind to their internal receptors, allowing them to directly affect the cell's DNA and protein-producing machinery. Using signal transduction pathways, receptors in the plasma membrane produce a variety of effects on the cell. The results of signaling pathways are extremely varied and depend on the type of cell involved as well as the external and internal conditions. A small sampling of responses is described below.

Gene Expression

Some signal transduction pathways regulate the transcription of RNA. Others regulate the translation of proteins from mRNA. An example of a protein that regulates translation in the nucleus is the MAP kinase ERK. ERK is activated in a phosphorylation cascade when epidermal growth factor (EGF) binds the EGF receptor (see [link]). Upon phosphorylation, ERK enters the nucleus and activates a protein kinase that, in turn, regulates protein translation ([link]).

The MAP kinase ERK phosphorylates MNK1. MNK1 in turn phosphorylates eIF-4E, which is associated with mRNA. The mRNA unfolds and protein sythesis begins.

ERK is a MAP kinase that activates translation when it is phosphorylated. ERK phosphorylates MNK1, which in turn phosphorylates eIF-4E, an elongation initiation factor that, with other initiation factors, is associated with mRNA. When eIF-4E becomes phosphorylated, the mRNA unfolds, allowing protein synthesis in the nucleus to begin. (See [link] for the phosphorylation pathway that activates ERK.)

The second kind of protein with which PKC can interact is a protein that acts as an inhibitor. An **inhibitor** is a molecule that binds to a protein and prevents it from functioning or reduces its function. In this case, the

inhibitor is a protein called Iκ-B, which binds to the regulatory protein NF-κB. (The symbol κ represents the Greek letter kappa.) When Iκ-B is bound to NF-κB, the complex cannot enter the nucleus of the cell, but when Iκ-B is phosphorylated by PKC, it can no longer bind NF-κB, and NF-κB (a transcription factor) can enter the nucleus and initiate RNA transcription. In this case, the effect of phosphorylation is to inactivate an inhibitor and thereby activate the process of transcription.

Increase in Cellular Metabolism

The result of another signaling pathway affects muscle cells. The activation of β-adrenergic receptors in muscle cells by adrenaline leads to an increase in cyclic AMP (cAMP) inside the cell. Also known as epinephrine, adrenaline is a hormone (produced by the adrenal gland attached to the kidney) that readies the body for short-term emergencies. Cyclic AMP activates PKA (protein kinase A), which in turn phosphorylates two enzymes. The first enzyme promotes the degradation of glycogen by activating intermediate glycogen phosphorylase kinase (GPK) that in turn activates glycogen phosphorylase (GP) that catabolizes glycogen into glucose. (Recall that your body converts excess glucose to glycogen for short-term storage. When energy is needed, glycogen is quickly reconverted to glucose.) Phosphorylation of the second enzyme, glycogen synthase (GS), inhibits its ability to form glycogen from glucose. In this manner, a muscle cell obtains a ready pool of glucose by activating its formation via glycogen degradation and by inhibiting the use of glucose to form glycogen, thus preventing a futile cycle of glycogen degradation and synthesis. The glucose is then available for use by the muscle cell in response to a sudden surge of adrenaline—the "fight or flight" reflex.

Cell Growth

Cell signaling pathways also play a major role in cell division. Cells do not normally divide unless they are stimulated by signals from other cells. The ligands that promote cell growth are called **growth factors**. Most growth factors bind to cell-surface receptors that are linked to tyrosine kinases. These cell-surface receptors are called receptor tyrosine kinases (RTKs).

Activation of RTKs initiates a signaling pathway that includes a G-protein called RAS, which activates the MAP kinase pathway described earlier. The enzyme MAP kinase then stimulates the expression of proteins that interact with other cellular components to initiate cell division.

Note:
Career Connection
Cancer Biologist
Cancer biologists study the molecular origins of cancer with the goal of developing new prevention methods and treatment strategies that will inhibit the growth of tumors without harming the normal cells of the body. As mentioned earlier, signaling pathways control cell growth. These signaling pathways are controlled by signaling proteins, which are, in turn, expressed by genes. Mutations in these genes can result in malfunctioning signaling proteins. This prevents the cell from regulating its cell cycle, triggering unrestricted cell division and cancer. The genes that regulate the signaling proteins are one type of oncogene which is a gene that has the potential to cause cancer. The gene encoding RAS is an oncogene that was originally discovered when mutations in the RAS protein were linked to cancer. Further studies have indicated that 30 percent of cancer cells have a mutation in the RAS gene that leads to uncontrolled growth. If left unchecked, uncontrolled cell division can lead tumor formation and metastasis, the growth of cancer cells in new locations in the body. Cancer biologists have been able to identify many other oncogenes that contribute to the development of cancer. For example, HER2 is a cell-surface receptor that is present in excessive amounts in 20 percent of human breast cancers. Cancer biologists realized that gene duplication led to HER2 overexpression in 25 percent of breast cancer patients and developed a drug called Herceptin (trastuzumab). Herceptin is a monoclonal antibody that targets HER2 for removal by the immune system. Herceptin therapy helps to control signaling through HER2. The use of Herceptin in combination with chemotherapy has helped to increase the overall survival rate of patients with metastatic breast cancer.
More information on cancer biology research can be found at the National Cancer Institute website

Cell Death

When a cell is damaged, superfluous, or potentially dangerous to an organism, a cell can initiate a mechanism to trigger programmed cell death, or **apoptosis**. Apoptosis allows a cell to die in a controlled manner that prevents the release of potentially damaging molecules from inside the cell. There are many internal checkpoints that monitor a cell's health; if abnormalities are observed, a cell can spontaneously initiate the process of apoptosis. However, in some cases, such as a viral infection or uncontrolled cell division due to cancer, the cell's normal checks and balances fail. External signaling can also initiate apoptosis. For example, most normal animal cells have receptors that interact with the extracellular matrix, a network of glycoproteins that provides structural support for cells in an organism. The binding of cellular receptors to the extracellular matrix initiates a signaling cascade within the cell. However, if the cell moves away from the extracellular matrix, the signaling ceases, and the cell undergoes apoptosis. This system keeps cells from traveling through the body and proliferating out of control, as happens with tumor cells that metastasize.

Another example of external signaling that leads to apoptosis occurs in T-cell development. T-cells are immune cells that bind to foreign macromolecules and particles, and target them for destruction by the immune system. Normally, T-cells do not target "self" proteins (those of their own organism), a process that can lead to autoimmune diseases. In order to develop the ability to discriminate between self and non-self, immature T-cells undergo screening to determine whether they bind to so-called self proteins. If the T-cell receptor binds to self proteins, the cell initiates apoptosis to remove the potentially dangerous cell.

Apoptosis is also essential for normal embryological development. In vertebrates, for example, early stages of development include the formation of web-like tissue between individual fingers and toes ([link]). During the

course of normal development, these unneeded cells must be eliminated, enabling fully separated fingers and toes to form. A cell signaling mechanism triggers apoptosis, which destroys the cells between the developing digits.

The histological section of a foot of a 15-day-old mouse embryo, visualized using light microscopy, reveals areas of tissue between the toes, which apoptosis will eliminate before the mouse reaches its full gestational age at 27 days. (credit: modification of

work by Michal
Mañas)

Termination of the Signal Cascade

The aberrant signaling often seen in tumor cells is proof that the termination of a signal at the appropriate time can be just as important as the initiation of a signal. One method of stopping a specific signal is to degrade the ligand or remove it so that it can no longer access its receptor. One reason that hydrophobic hormones like estrogen and testosterone trigger long-lasting events is because they bind carrier proteins. These proteins allow the insoluble molecules to be soluble in blood, but they also protect the hormones from degradation by circulating enzymes.

Inside the cell, many different enzymes reverse the cellular modifications that result from signaling cascades. For example, **phosphatases** are enzymes that remove the phosphate group attached to proteins by kinases in a process called dephosphorylation. Cyclic AMP (cAMP) is degraded into AMP by **phosphodiesterase**, and the release of calcium stores is reversed by the Ca^{2+} pumps that are located in the external and internal membranes of the cell.

Section Summary

The initiation of a signaling pathway is a response to external stimuli. This response can take many different forms, including protein synthesis, a change in the cell's metabolism, cell growth, or even cell death. Many pathways influence the cell by initiating gene expression, and the methods utilized are quite numerous. Some pathways activate enzymes that interact with DNA transcription factors. Others modify proteins and induce them to change their location in the cell. Depending on the status of the organism, cells can respond by storing energy as glycogen or fat, or making it available in the form of glucose. A signal transduction pathway allows muscle cells to respond to immediate requirements for energy in the form of glucose. Cell growth is almost always stimulated by external signals called growth factors. Uncontrolled cell growth leads to cancer, and mutations in

the genes encoding protein components of signaling pathways are often found in tumor cells. Programmed cell death, or apoptosis, is important for removing damaged or unnecessary cells. The use of cellular signaling to organize the dismantling of a cell ensures that harmful molecules from the cytoplasm are not released into the spaces between cells, as they are in uncontrolled death, necrosis. Apoptosis also ensures the efficient recycling of the components of the dead cell. Termination of the cellular signaling cascade is very important so that the response to a signal is appropriate in both timing and intensity. Degradation of signaling molecules and dephosphorylation of phosphorylated intermediates of the pathway by phosphatases are two ways to terminate signals within the cell.

Review Questions

Exercise:

   Problem: What is the function of a phosphatase?

   a. A phosphatase removes phosphorylated amino acids from proteins.
   b. A phosphatase removes the phosphate group from phosphorylated amino acid residues in a protein.
   c. A phosphatase phosphorylates serine, threonine, and tyrosine residues.
   d. A phosphatase degrades second messengers in the cell.

   Solution:

   B

Exercise:

   Problem: How does NF-κB induce gene expression?

   a. A small, hydrophobic ligand binds to NF-κB, activating it.

b. Phosphorylation of the inhibitor Iκ-B dissociates the complex between it and NF-κB, and allows NF-κB to enter the nucleus and stimulate transcription.
c. NF-κB is phosphorylated and is then free to enter the nucleus and bind DNA.
d. NF-κB is a kinase that phosphorylates a transcription factor that binds DNA and promotes protein production.

Solution:

B

Exercise:

Problem:

Apoptosis can occur in a cell when the cell is _____.

a. damaged
b. no longer needed
c. infected by a virus
d. all of the above

Solution:

D

Exercise:

Problem: What is the effect of an inhibitor binding an enzyme?

a. The enzyme is degraded.
b. The enzyme is activated.
c. The enzyme is inactivated.
d. The complex is transported out of the cell.

Solution:

C

Free Response

Exercise:

Problem:

What is a possible result of a mutation in a kinase that controls a pathway that stimulates cell growth?

Solution:

If a kinase is mutated so that it is always activated, it will continuously signal through the pathway and lead to uncontrolled growth and possibly cancer. If a kinase is mutated so that it cannot function, the cell will not respond to ligand binding.

Exercise:

Problem:

How does the extracellular matrix control the growth of cells?

Solution:

Receptors on the cell surface must be in contact with the extracellular matrix in order to receive positive signals that allow the cell to live. If the receptors are not activated by binding, the cell will undergo apoptosis. This ensures that cells are in the correct place in the body and helps to prevent invasive cell growth as occurs in metastasis in cancer.

Glossary

apoptosis
    programmed cell death

growth factor
      ligand that binds to cell-surface receptors and stimulates cell growth

inhibitor
      molecule that binds to a protein (usually an enzyme) and keeps it from
      functioning

phosphatase
      enzyme that removes the phosphate group from a molecule that has
      been previously phosphorylated

phosphodiesterase
      enzyme that degrades cAMP, producing AMP, to terminate signaling

Signaling in Single-Celled Organisms
By the end of this section, you will be able to:

- Describe how single-celled yeasts use cell signaling to communicate with one another
- Relate the role of quorum sensing to the ability of some bacteria to form biofilms

Within-cell signaling allows bacteria to respond to environmental cues, such as nutrient levels, some single-celled organisms also release molecules to signal to each other.

Signaling in Yeast

Yeasts are eukaryotes (fungi), and the components and processes found in yeast signals are similar to those of cell-surface receptor signals in multicellular organisms. Budding yeasts ([link]) are able to participate in a process that is similar to sexual reproduction that entails two haploid cells (cells with one-half the normal number of chromosomes) combining to form a diploid cell (a cell with two sets of each chromosome, which is what normal body cells contain). In order to find another haploid yeast cell that is prepared to mate, budding yeasts secrete a signaling molecule called **mating factor**. When mating factor binds to cell-surface receptors in other yeast cells that are nearby, they stop their normal growth cycles and initiate a cell signaling cascade that includes protein kinases and GTP-binding proteins that are similar to G-proteins.
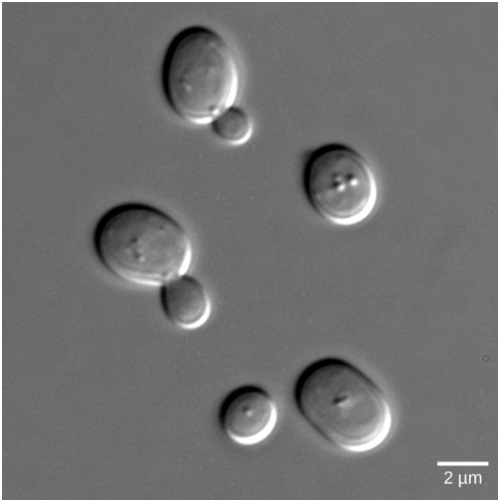
Budding *Saccharomyces cerevisiae* yeast cells can communicate by releasing a signaling molecule called mating factor. In this micrograph, they are visualized using differential interference contrast microscopy, a light microscopy technique that enhances the contrast of the sample.

Signaling in Bacteria

Signaling in bacteria enables bacteria to monitor extracellular conditions, ensure that there are sufficient amounts of nutrients, and ensure that hazardous situations are avoided. There are circumstances, however, when bacteria communicate with each other.
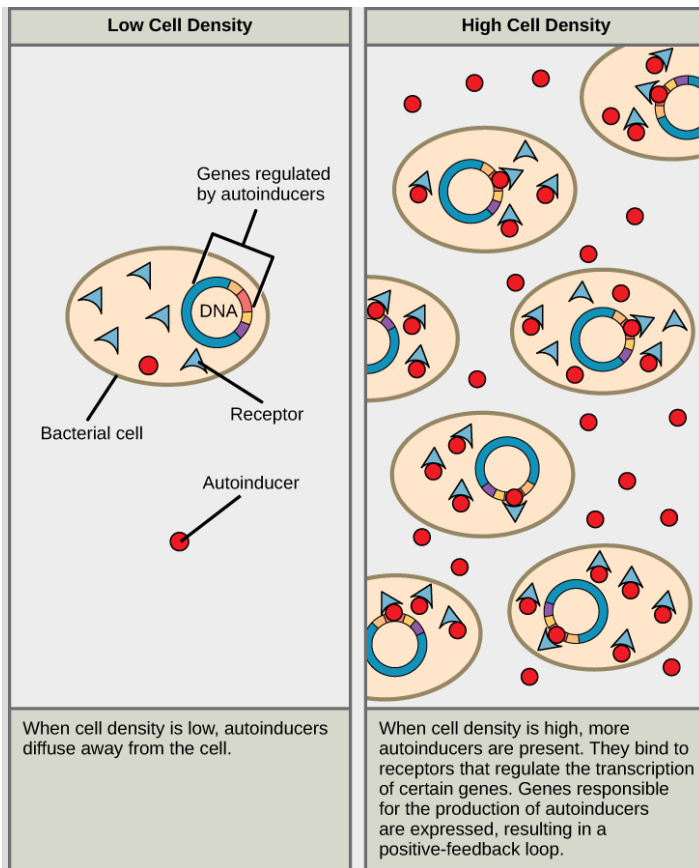
The first evidence of bacterial communication was observed in a bacterium that has a symbiotic relationship with Hawaiian bobtail squid. When the

population density of the bacteria reaches a certain level, specific gene expression is initiated, and the bacteria produce bioluminescent proteins that emit light. Because the number of cells present in the environment (cell density) is the determining factor for signaling, bacterial signaling was named **quorum sensing**. In politics and business, a quorum is the minimum number of members required to be present to vote on an issue.

Quorum sensing uses autoinducers as signaling molecules. **Autoinducers** are signaling molecules secreted by bacteria to communicate with other bacteria of the same kind. The secreted autoinducers can be small, hydrophobic molecules such as acyl-homoserine lactone, (AHL) or larger peptide-based molecules; each type of molecule has a different mode of action. When AHL enters target bacteria, it binds to transcription factors, which then switch gene expression on or off ([link]). The peptide autoinducers stimulate more complicated signaling pathways that include bacterial kinases. The changes in bacteria following exposure to autoinducers can be quite extensive. The pathogenic bacterium *Pseudomonas aeruginosa* has 616 different genes that respond to autoinducers.

Note:
Art Connection

Low Cell Density	High Cell Density
Genes regulated by autoinducers	
DNA	
Receptor	
Bacterial cell	
Autoinducer	
When cell density is low, autoinducers diffuse away from the cell.	When cell density is high, more autoinducers are present. They bind to receptors that regulate the transcription of certain genes. Genes responsible for the production of autoinducers are expressed, resulting in a positive-feedback loop.

Autoinducers are small molecules or proteins produced by bacteria that regulate gene expression.

Which of the following statements about quorum sensing is false?

   a. Autoinducer must bind to receptor to turn on transcription of genes responsible for the production of more autoinducer.
   b. The receptor stays in the bacterial cell, but the autoinducer diffuses out.
   c. Autoinducer can only act on a different cell: it cannot act on the cell in which it is made.
   d. Autoinducer turns on genes that enable the bacteria to form a biofilm.

Some species of bacteria that use quorum sensing form biofilms, complex colonies of bacteria (often containing several species) that exchange chemical signals to coordinate the release of toxins that will attack the host. Bacterial biofilms ([link]) can sometimes be found on medical equipment; when biofilms invade implants such as hip or knee replacements or heart pacemakers, they can cause life-threatening infections.

Note:

Art Connection
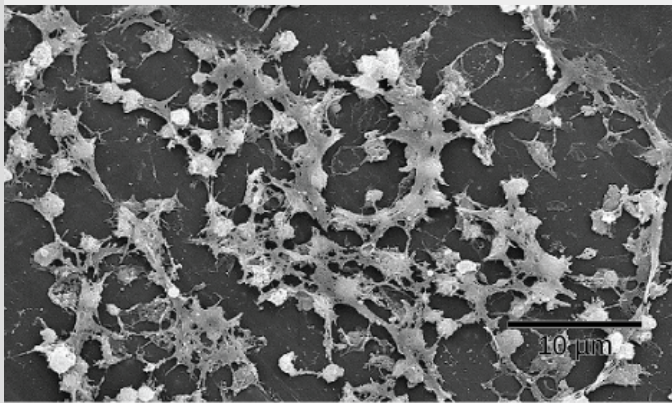
(a)   (b)

Cell-cell communication enables these (a) *Staphylococcus aureus* bacteria to work together to form a biofilm inside a hospital patient's catheter, seen here via scanning electron microscopy. *S. aureus* is the main cause of hospital-acquired infections. (b) Hawaiian bobtail squid have a symbiotic relationship with the bioluminescent bacteria *Vibrio fischeri*. The luminescence makes it difficult to see the squid from below because it effectively eliminates its shadow. In return for camouflage, the squid provides food for the bacteria. Free-living *V. fischeri* do not produce luciferase, the enzyme responsible for luminescence, but *V. fischeri* living in a symbiotic relationship with the squid do. Quorum sensing determines whether the bacteria should produce the luciferase enzyme. (credit a: modifications of

work by CDC/Janice Carr; credit b: modifications of work by Cliff1066/Flickr)

What advantage might biofilm production confer on the *S. aureus* inside the catheter?

Research on the details of quorum sensing has led to advances in growing bacteria for industrial purposes. Recent discoveries suggest that it may be possible to exploit bacterial signaling pathways to control bacterial growth; this process could replace or supplement antibiotics that are no longer effective in certain situations.

Note:
Link to Learning

Watch geneticist Bonnie Bassler discuss her [discovery](#) of quorum sensing in biofilm bacteria in squid.

Note:
Evolution Connection
Cellular Communication in Yeasts
The first life on our planet consisted of single-celled prokaryotic organisms that had limited interaction with each other. While some external signaling occurs between different species of single-celled organisms, the majority of signaling within bacteria and yeasts concerns only other members of the same species. The evolution of cellular communication is an absolute

necessity for the development of multicellular organisms, and this innovation is thought to have required approximately 2.5 billion years to appear in early life forms.

Yeasts are single-celled eukaryotes, and therefore have a nucleus and organelles characteristic of more complex life forms. Comparisons of the genomes of yeasts, nematode worms, fruit flies, and humans illustrate the evolution of increasingly complex signaling systems that allow for the efficient inner workings that keep humans and other complex life forms functioning correctly.

Kinases are a major component of cellular communication, and studies of these enzymes illustrate the evolutionary connectivity of different species. Yeasts have 130 types of kinases. More complex organisms such as nematode worms and fruit flies have 454 and 239 kinases, respectively. Of the 130 kinase types in yeast, 97 belong to the 55 subfamilies of kinases that are found in other eukaryotic organisms. The only obvious deficiency seen in yeasts is the complete absence of tyrosine kinases. It is hypothesized that phosphorylation of tyrosine residues is needed to control the more sophisticated functions of development, differentiation, and cellular communication used in multicellular organisms.

Because yeasts contain many of the same classes of signaling proteins as humans, these organisms are ideal for studying signaling cascades. Yeasts multiply quickly and are much simpler organisms than humans or other multicellular animals. Therefore, the signaling cascades are also simpler and easier to study, although they contain similar counterparts to human signaling.[footnote]

G. Manning, G.D. Plowman, T. Hunter, S. Sudarsanam, "Evolution of Protein Kinase Signaling from Yeast to Man," *Trends in Biochemical Sciences* 27, no. 10 (2002): 514–520.

Note:
Link to Learning

Watch this collection of interview clips with biofilm researchers in "What Are Bacterial Biofilms?"
https://www.openstaxcollege.org/l/bacteria_bioflm

Section Summary

Yeasts and multicellular organisms have similar signaling mechanisms. Yeasts use cell-surface receptors and signaling cascades to communicate information on mating with other yeast cells. The signaling molecule secreted by yeasts is called mating factor.

Bacterial signaling is called quorum sensing. Bacteria secrete signaling molecules called autoinducers that are either small, hydrophobic molecules or peptide-based signals. The hydrophobic autoinducers, such as AHL, bind transcription factors and directly affect gene expression. The peptide-based molecules bind kinases and initiate signaling cascades in the cells.

Art Connections

Exercise:

Problem:

[link] Which of the following statements about quorum sensing is false?

    a. Autoinducer must bind to receptor to turn on transcription of genes responsible for the production of more autoinducer.
    b. The receptor stays in the bacterial cell, but the autoinducer diffuses out.

c. Autoinducer can only act on a different cell: it cannot act on the cell in which it is made.
d. Autoinducer turns on genes that enable the bacteria to form a biofilm.

Solution:

[link] C.

Exercise:

Problem:

[link] What advantage might biofilm production confer on the *S. aureus* inside the catheter?

Solution:

[link] *S. aureus* produces a biofilm because the higher cell density in the biofilm permits the formation of a dense surface that helps protect the bacteria from antibiotics.

Review Questions

Exercise:

Problem:

Which type of molecule acts as a signaling molecule in yeasts?

a. steroid
b. autoinducer
c. mating factor
d. second messenger

Solution:

C

Exercise:

Problem: Quorum sensing is triggered to begin when _____.

    a. treatment with antibiotics occurs
    b. bacteria release growth hormones
    c. bacterial protein expression is switched on
    d. a sufficient number of bacteria are present

Solution:

D

Free Response

Exercise:

Problem:

What characteristics make yeasts a good model for learning about signaling in humans?

Solution:

Yeasts are eukaryotes and have many of the same systems that humans do; however, they are single-celled, so they are easy to grow, grow rapidly, have a short generation time, and are much simpler than humans.

Exercise:

Problem:

Why is signaling in multicellular organisms more complicated than signaling in single-celled organisms?

Solution:

Multicellular organisms must coordinate many different events in different cell types that may be very distant from each other. Single-celled organisms are only concerned with their immediate environment and the presence of other cells in the area.

Glossary

autoinducer
    signaling molecule secreted by bacteria to communicate with other bacteria of its kind and others

mating factor
    signaling molecule secreted by yeast cells to communicate to nearby yeast cells that they are available to mate and communicating their mating orientation

quorum sensing
    method of cellular communication used by bacteria that informs them of the abundance of similar (or different) bacteria in the environment

The Periodic Table of Elements

Periodic Table of the Elements

Group 1	2		3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18

Row 1:
1 H 1.01 Hydrogen — 2 He 4.00 Helium

Row 2:
3 Li 6.94 Lithium | 4 Be 9.01 Beryllium | 5 B 10.81 Boron | 6 C 12.11 Carbon | 7 N 14.01 Nitrogen | 8 O 15.99 Oxygen | 9 F 18.99 Fluorine | 10 Ne 20.18 Neon

Row 3:
11 Na 22.99 Sodium | 12 Mg 24.31 Magnesium | 13 Al 26.98 Aluminum | 14 Si 28.09 Silicon | 15 P 30.97 Phosphorus | 16 S 32.07 Sulfur | 17 Cl 35.45 Chlorine | 18 Ar 39.95 Argon

Row 4:
19 K 39.09 Potassium | 20 Ca 40.08 Calcium | 21 Sc 44.96 Scandium | 22 Ti 47.87 Titanium | 23 V 50.94 Vanadium | 24 Cr 51.99 Chromium | 25 Mn 54.94 Manganese | 26 Fe 55.85 Iron | 27 Co 58.93 Cobalt | 28 Ni 58.69 Nickel | 29 Cu 63.55 Copper | 30 Zn 65.41 Zinc | 31 Ga 69.72 Gallium | 32 Ge 72.64 Germanium | 33 As 74.92 Arsenic | 34 Se 78.96 Selenium | 35 Br 79.90 Bromine | 36 Kr 83.79 Krypton

Row 5:
37 Rb 85.47 Rubidium | 38 Sr 87.62 Strontium | 39 Y 88.91 Yttrium | 40 Zr 91.22 Zirconium | 41 Nb 92.91 Niobium | 42 Mo 95.94 Molybdenum | 43 Tc [98] Technetium | 44 Ru 101.1 Ruthenium | 45 Rh 102.9 Rhodium | 46 Pd 106.4 Palladium | 47 Ag 107.9 Silver | 48 Cd 112.4 Cadmium | 49 In 114.8 Indium | 50 Sn 118.7 Tin | 51 Sb 121.8 Antimony | 52 Te 127.6 Tellurium | 53 I 126.9 Iodine | 54 Xe 131.3 Xenon

Row 6:
55 Cs 132.9 Cesium | 56 Ba 137.3 Barium | 57-71 La–Lu * | 72 Hf 178.5 Hafnium | 73 Ta 180.9 Tantalum | 74 W 183.8 Tungsten | 75 Re 186.2 Rhenium | 76 Os 190.2 Osmium | 77 Ir 192.2 Iridium | 78 Pt 195.1 Platinum | 79 Au 196.9 Gold | 80 Hg 200.6 Mercury | 81 Tl 204.4 Thallium | 82 Pb 207.2 Lead | 83 Bi 208.9 Bismuth | 84 Po [209] Polonium | 85 At [210] Astatine | 86 Rn [222] Radon

Row 7:
87 Fr [223] Francium | 88 Ra [226] Radium | 89-103 Ac–Lr ** | 104 Rf [261] Rutherfordium | 105 Db [262] Dubnium | 106 Sg [266] Seaborgium | 107 Bh [264] Bohrium | 108 Hs [277] Hassium | 109 Mt [268] Meitnerium | 110 Ds [269] Darmstadtium | 111 Rg [272] Roentgenium | 112 Cn [285] Copernicium | 113 Uut [284] Ununtrium | 114 Fl [289] Flerovium | 115 Uup [288] Ununpentium | 116 Lv [293] Livermorium | 117 Uus [294] Ununseptium | 118 Uuo [294] Ununoctium

* Lanthanides:
57 La 138.9 Lanthanum | 58 Ce 140.1 Cerium | 59 Pr 140.9 Praseodymium | 60 Nd 144.2 Neodymium | 61 Pm [145] Promethium | 62 Sm 150.4 Samarium | 63 Eu 151.9 Europium | 64 Gd 157.3 Gadolinium | 65 Tb 158.9 Terbium | 66 Dy 162.5 Dysprosium | 67 Ho 164.9 Holmium | 68 Er 167.3 Erbium | 69 Tm 168.9 Thulium | 70 Yb 173.1 Ytterbium | 71 Lu 174.9 Lutetium

** Actinides:
89 Ac [227] Actinium | 90 Th 232.0 Thorium | 91 Pa 231.0 Protactinium | 92 U 238.0 Uranium | 93 Np [237] Neptunium | 94 Pu [244] Plutonium | 95 Am [243] Americium | 96 Cm [247] Curium | 97 Bk [247] Berkelium | 98 Cf [251] Californium | 99 Es [252] Einsteinium | 100 Fm [257] Fermium | 101 Md [258] Mendelevium | 102 No [259] Nobelium | 103 Lr [262] Lawrencium

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Atomic Number → 1

H ← Symbol

1.01 ← Relative Atomic Mass

Name → Hydrogen

Color Code

- Other non-metals
- Alkali metals
- Transition metals
- Other metals
- Alkaline earth metals
- Halogens
- Noble gases
- Lanthanides
- Actinides
- Unknown chemical properties